CLINICAL AT

FERGIcor, a Randomized Controlled Trial on Ferric Carboxymaltose for Iron Deficiency Anemia in Inflammatory Bowel Disease

RAYKO EVSTATIEV,* PHILIPPE MARTEAU,‡ TARIQ IQBAL,§ IGOR L. KHALIF,‖ JÜRGEN STEIN,¶ BERND BOKEMEYER,# IVAN V. CHOPEY,** FLORIAN S. GUTZWILLER,‡‡ LISE RIOPEL,§§ and CHRISTOPH GASCHE,* for the FERGI Study Group

*Department of Medicine 3, Division of Gastroenterology and Hepatology, Christian Doppler Laboratory for Molecular Cancer Chemoprevention, Medical University of Vienna, Vienna, Austria; ‡AP-HP, Département medico-chirurgical de pathologie digestive Hôpital Lariboisière & Université Denis Diderot- Paris 7, Paris, France; §University Hospital, Birmingham, United Kingdom; ‖State Scientific Centre of Coloproctology, Moscow, Russia; ¶Department of Gastroenterology and Clinical Nutrition and Crohn Colitis Centre Rhein Main, Frankfurt/Main, Germany; #Gastroenterologische Gemeinschaftspraxis, Minden, Germany; **National University, Uzhgorod, Ukraine; ‡‡Institute of Pharmaceutical Medicine (ECPM), University of Basel, Basel, Switzerland; and §§Vifor Pharma, Glattbrugg, Switzerland

See Covering the Cover synopsis on page 783.

BACKGROUND & AIMS: Iron deficiency anemia (IDA) is common in chronic diseases and intravenous iron is an effective and recommended treatment. However, dose calculations and inconvenient administration may affect compliance and efficacy. We compared the efficacy and safety of a novel fixed-dose ferric carboxymaltose regimen (FCM) with individually calculated iron sucrose (IS) doses in patients with inflammatory bowel disease (IBD) and IDA. **METHODS:** This randomized, controlled, open-label, multicenter study included 485 patients with IDA (ferritin <100 μg/L, hemoglobin [Hb] 7–12 g/dL [female] or 7–13 g/dL [male]) and mild-to-moderate or quiescent IBD at 88 hospitals and clinics in 14 countries. Patients received either FCM in a maximum of 3 infusions of 1000 or 500 mg iron, or Ganzoni-calculated IS dosages in up to 11 infusions of 200 mg iron. Primary end point was Hb response (Hb increase ≥2 g/dL); secondary end points included anemia resolution and iron status normalization by week 12. **RESULTS:** The results of 240 FCM-treated and 235 IS-treated patients were analyzed. More patients with FCM than IS achieved Hb response (150 [65.8%] vs 118 [53.6%]; 12.2% difference, $P = .004$) or Hb normalization (166 [72.8%] vs 136 [61.8%]; 11.0% difference, $P = .015$). Both treatments improved quality of life scores by week 12. Study drugs were well tolerated and drug-related adverse events were in line with drug-specific clinical experience. Deviations from scheduled total iron dosages were more frequent in the IS group. **CONCLUSIONS:** The simpler FCM-based dosing regimen showed better efficacy and compliance, as well as a good safety profile, compared with the Ganzoni-calculated IS dose regimen.

Keywords: Intravenous Iron; Crohn's Disease; Ulcerative Colitis.

View this article's video abstract at www.gastrojournal.org.

Iron deficiency and iron deficiency anemia (IDA) are frequent conditions in the general population[1] and present particularly often in patients with chronic diseases such as inflammatory bowel disease (IBD), rheumatoid arthritis, chronic kidney disease, chronic heart failure, and cancer.[2,3] Iron deficiency is an important cause of anemia, which in turn can trigger hospitalization and even mortality.[4] Furthermore, anemia affects cardiac function and quality of life substantially.[5,6] Iron deficiency even without anemia is associated with fatigue[7] as well as impaired physical performance[8] and cognitive function.[4,6,9]

The main cause of a negative iron balance in patients with chronic diseases is impaired absorption and utilization of nutritional or orally administered iron.[10] Proinflammatory cytokines up-regulate hepcidin, a key mediator in iron homeostasis that blocks the release of iron from enterocytes and macrophages and can lead to anemia of chronic disease.[10] The shortage of iron can be aggravated by chronic blood loss leading to absolute iron deficiency and IDA. Management of iron deficiency by addressing iron availability and iron stores is critical. IBD is a model for such a condition with the prevalence of iron deficiency in IBD ranging from 36% to 90%.[2,11]

Improvement of hemoglobin (Hb) and iron status (ie, serum ferritin and transferrin saturation) in anemic IBD patients can be achieved with systemic iron treatment[12,13] and is associated with improved quality of life scores independent of changes in disease activity.[6] In addition, iron deficiency is frequently associated with secondary thrombocytosis,[14] adding a potential risk of thromboembolic events to these patients.[15] Iron repletion and resolution of anemia may normalize the increased platelet counts.[16]

International guidelines for the management of anemia associated with IBD recommend intravenous iron replacement therapy as the preferred route of iron administration.[17] Intravenous iron is more effective, better tolerated, and improves the quality of life to a greater extent than oral iron supplements.[13,17-19] Most clinical trials have used iron sucrose (IS) to evaluate efficacy and safety of intra-

Abbreviations used in this paper: CI, confidence interval; FCM, ferric carboxymaltose; Hb, hemoglobin; IBDQ, inflammatory bowel disease questionnaire; IDA, iron deficiency anemia; IS, iron sucrose; OR, odds ratio; SF-36, health survey short form; SD, standard deviation; TSAT, transferrin saturation.

0016-5085/$36.00
doi:10.1053/j.gastro.2011.06.005

venous iron therapy. IS was effective in 50%–91% of IBD patients depending on the study criteria.[2] A recently reported randomized, controlled, multicenter study showed that intravenous IS treatment is superior to oral iron in correcting Hb and iron stores in IBD patients.[18] In clinical practice, IS proved to be an effective and well-tolerated intravenous iron preparation.[17,20,21]

A constraint of IS is the dose limitation of 200 mg iron per infusion because, in an IBD clinic, most anemic patients will have an iron deficit of 1000 mg or more. Thus, multiple infusions are required to replenish iron stores and correct IDA. Ferric carboxymaltose (FCM) is an intravenous iron preparation that can be administered in single doses of up to 1000 mg iron within 15 minutes. The efficacy and tolerability of FCM have been shown in various indications, including anemia associated with IBD,[13] postpartum phase,[22] heavy uterine bleeding,[23] and most recently in chronic heart failure.[5]

In current practice, the Ganzoni formula is used to calculate individual iron need.[24] However, this formula is inconvenient, prone to errors, inconsistently used in clinical practice, and underestimates iron requirements.[13] Here, we evaluated whether a novel and simple dosing regimen of FCM is at least as effective and safe as the Ganzoni-calculated dosage of repeated IS infusions in anemic patients with mild or quiescent IBD.

Patients and Methods

Study Design and Patients

The study was designed as a randomized, controlled, multicenter, open-label trial testing a novel treatment regimen using FCM (Ferinject; Vifor Pharma, Glattbrugg, Switzerland) for noninferiority compared with the Ganzoni-calculated doses of IS (Venofer; Vifor Pharma, Glattbrugg, Switzerland) in patients with IBD and IDA. The study was conducted from October 2008 to December 2009 at 88 hospitals and clinics in 14 countries in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study was registered at ClinicalTrials.gov (NCT00810030) and run after approval of the protocol and its amendments by the concerned local ethics committees and competent authorities. No conflicts of interests were disclosed to study participants in the informed consent form.

Patients with iron deficiency anemia (Hb 7–12 g/dL [female] or 7–13 g/dL [male] and ferritin <100 μg/L) and mild to moderate IBD (Crohn's disease [CD] with a Crohn's disease activity index [CDAI] <220 or ulcerative colitis [UC] with a colitis activity index [CAI] ≤7) or IBD in remission (CDAI <150 or CAI ≤4) were recruited. Further inclusion criteria were normal levels of vitamin B-12 and folic acid. Eligible patients had to be 18 years of age or older and to have signed informed consent. Females of child-bearing potential had to have a negative urine pregnancy test at screening and had to use an acceptable method of birth control during the study and for up to 1 month after the last dose of the study drug. Patients with intravenous or oral iron treatment or blood transfusions within 4 weeks prior to screening or history of erythropoietin treatment were excluded. Further exclusion criteria comprised chronic alcohol abuse; chronic liver disease or increase of transaminases more than 3 times above the normal upper range limit; presence of portal hypertension with esophageal varices; known hypersensitivity to the study drug; history of acquired iron overload; myelodysplastic syndrome; pregnancy or lactation; known active infection; clinically significant overt bleeding; active malignancy or chronic renal failure; surgery with relevant blood loss (Hb decrease <2 g/dL) in the 3 months prior to screening or planned surgery within the following 3 months; known human immunodeficiency virus; hepatitis B or hepatitis C virus infection; significant cardiovascular disease; body weight <35 kg; and participation in any other interventional study within 1 month prior to screening.

Randomization

Patients were randomized 1:1 to each of the treatment arms according to a predefined, computer-generated list and stratified by gender and disease (CD/UC) as provided via sequentially numbered randomization envelopes by data management, PAREXEL International GmbH. Both participants and physicians were aware of which treatment was being administered.

Treatment Schedule

The selection of FCM total dosages was based on predefined cut-offs for baseline Hb levels and body weight (Table 1). FCM was administered in single, once weekly infusions of 1000 mg or 500 mg iron over at least 15 minutes on day 1 and, if needed, days 8 and 15. Patients with a body weight <67 kg received a maximum of 500 mg iron per infusion. The IS regimen was calculated for each patient individually by the Ganzoni formula (total iron dose = [body weight × (target Hb – actual Hb)] × 2.4 + iron storage depot) and comprised up to 11 infusions of 200 mg iron over at least 30 minutes given up to twice weekly (target Hb level 15 g/dL, iron storage depot 500 mg).

Outcome Measures

The primary end point was the number of Hb responders as defined by an Hb increase ≥2 g/dL at week 12 compared with baseline levels. Secondary efficacy end points comprised the proportions of patients achieving normalization of Hb (≥12 g/dL in female, ≥13 g/dL in male patients), transferrin saturation (TSAT; 20%–50%), and ferritin (≥100 μg/L) at week 12 as well as repeated measure analyses of changes in Hb, TSAT, and ferritin from baseline to subsequent visits.

Further secondary parameters were the proportion of patients who were no longer anemic or achieved an Hb increase ≥2 g/dL, who were no longer anemic and achieved ferritin >100 μg/L, as well as changes in health-related quality of life, which was assessed using the Health Survey Short Form (SF-36), version 2,[25] and Inflammatory Bowel Disease Questionnaire (IBDQ) scores[26] from baseline to week 12.

Follow-up and Safety Evaluation

Patients in both groups were evaluated at weeks 1, 2, 4, 8, and 12. At each visit, blood tests were performed, and adverse

Table 1. Total Iron Dose With the FCM Dose Regimen

Hb (g/dL)	Body weight <70 kg	Body weight ≥70 kg
≥10	1000 mg	1500 mg
7–10	1500 mg	2000 mg

NOTE. Total dosage was administered in single infusions of 500 mg or 1000 mg iron as FCM. For patients with a body weight <67 kg, single doses of 500 mg were given.