Intravenous Ferric Carboxymaltose in Children with Iron Deficiency Anemia Who Respond Poorly to Oral Iron

Jacquelyn M. Powers, MD, MS[1,2,3], Mark Shamoun, MD[4,5], Timothy L. McCavit, MD, MS[6,7], Leah Adix, CCRP[5], and George R. Buchanan, MD[4,5,8]

Objective To assess the benefits and risks of intravenous (IV) ferric carboxymaltose (FCM) in children with iron deficiency anemia (IDA).

Study design In a retrospective cohort study of patients seen at our center, we identified all FCM infusions in children with IDA over a 12-month period through a query of pharmacy records. Clinical data, including hematologic response and adverse effects, were extracted from the electronic medical record.

Results A total of 116 IV FCM infusions were administered to 72 patients with IDA refractory to oral iron treatment (median age, 13.7 years; range, 9 months to 18 years). Median preinfusion and postinfusion hemoglobin values were 9.1 g/dL and 12.3 g/dL, respectively (at 4-12 weeks after the initial infusion; n = 53). Sixty-five patients (84%) experienced no adverse effects. Minor transient complications were encountered during or immediately after 7 infusions.

Conclusion FCM administered as a short IV infusion without a test dose proved to be safe and highly effective in a small yet diverse population of infants, children, and adolescents with IDA refractory to oral iron therapy. *(J Pediatr 2017;180:212-6).*

Intravenous (IV) iron is administered to many adults with iron-deficient erythropoiesis, yet this route of administration is infrequently used in children despite their high incidence of iron deficiency.[1] The primary causes of iron deficiency anemia (IDA) in children are reduced iron intake resulting from prolonged breastfeeding and/or excessive cow's milk intake in infants and heavy menstrual bleeding in adolescent females.[2,3] In infants, IDA is associated with neurocognitive impairment,[1,4,5] whereas affected adolescents report fatigue and poor concentration, which may contribute to diminished school achievement.[6-8]

Although standard initial therapy for IDA in children as well as adults is oral iron, many fail to respond owing to poor adherence, inadequate absorption, adverse effects, and/or failure to correct the primary etiology.[9,10] This results in repetitive, prolonged, and often ineffective treatment courses. Despite the remarkable advances in IV iron treatment strategies for adults, the use of parenteral iron in children is infrequent.[11,12] Safety concerns, high cost, and the need for "off-label" use have generally limited this route of administration only to children with chronic kidney disease or inflammatory bowel disease.[13]

Ferric carboxymaltose (FCM; Injectafer; American Regent, Shirley, New York) is a relatively new IV iron formulation approved for adults with IDA who are intolerant of or have an unsatisfactory response to oral iron. Unlike most other formulations of IV iron, FCM can be administered in 15 minutes without a previous test dose. Although FCM is relatively more expensive than alternative IV iron formulations, its much shorter infusion time decreases the ancillary costs of prolonged and/or multiple infusions and, accordingly, enhances patient convenience. In children, published data on FCM are limited to a single study in inflammatory bowel disease.[14] Given its favorable safety profile and the ease of its administration in adults, in 2014 FCM was added to our institution's formulary for off-label use in children with IDA who had failed oral iron therapy. Here we report the hematologic response and adverse effects in a cohort of infants, children, and adolescents with IDA who received FCM at our center.

Methods

This was a retrospective cohort study of patients with IDA who received FCM at Children's Medical Center in Dallas, Texas between June 1, 2014, and June 10, 2015. Patients were identified through a query of pharmacy records, and their characteristics and clinical data were abstracted from the electronic medical record.

IV	Intravenous
IDA	Iron deficiency anemia
FCM	Ferric carboxymaltose
Hgb	Hemoglobin

From the [1]Division of Hematology/Oncology; [2]Department of Pediatrics, Baylor College of Medicine, Houston, TX; [3]Texas Children's Hospital, Houston, TX; [4]Department of Pediatrics, The University of Texas Southwestern Medical Center, Dallas, TX; [5]Children's Health, Dallas, TX; [6]Division of Hematology/Oncology; [7]Department of Pediatrics, Cook Children's Hospital, Fort Worth, TX; and [8]Division of Hematology/Oncology, The University of Texas Southwestern Medical Center, Dallas, TX

Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award KL2TR001103. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors declare no conflicts of interest.

http://dx.doi.org10.1016/j.jpeds.2016.09.053

Patients without anemia who received FCM for other indications were excluded from the analysis. Our primary objectives were to define the hematologic response to FCM and to characterize the frequency, severity, and clinical features of its adverse effects. This study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center.

We developed a clinical protocol for administration of FCM following its addition to the hospital formulary using weight-based dosing (15 mg/kg; maximum 750 mg per dose). For patients weighing >50 kg, 2 doses (each up to 750 mg) were given at least 7 days apart (maximum total dose, 1500 mg). For patients weighing <50 kg, the decision to treat with 1 dose vs 2 doses was left to the discretion of the treating hematologist, a slight modification from the manufacturer's recommendation of 2 doses of 15 mg/kg given at least 7 days apart for all patients. All FCM infusions were administered with close monitoring and immediate availability of staff experienced with IV iron administration in either an outpatient day hospital/infusion setting or an inpatient setting when the patient had other indications for hospitalization.

FCM was administered over 15 minutes directly from a single-use vial via an infusion pump without routine premedication. Vital signs were assessed before the infusion, at 5 minutes after initiation of the infusion, on completion of the infusion, and again at 15 and 30 minutes postinfusion. Any reported adverse reactions prompted immediate assessment. Supportive care recommendations for the management of adverse events, such as nausea, urticaria, dyspnea, and/or anaphylaxis, were specified in the clinical protocol. All patients received a follow-up phone call within 24-72 hours after infusion to assess for delayed reactions.

Data collection included demographic information, specific indication for IV iron and/or etiology of iron deficiency, previous iron therapy (oral and/or IV), serial laboratory studies (at initial diagnosis and preinfusion and postinfusion), and FCM infusion information (ie, dosing, adverse effects with or without associated intervention). IDA was defined as microcytic anemia (based on patient age), a serum ferritin level <15 ng/mL, and/or total iron-binding capacity >425 μg/dL, if available. Hematologic response was assessed by subsequent hemoglobin (Hgb) concentration and mean corpuscular volume measurements, as well as serum ferritin level when available. Total iron deficit was calculated for all patients and compared with the total FCM dose administered.[15]

Response Criteria

In patients who had follow-up laboratory testing performed within 4-12 weeks after the initial infusion, we defined a complete response to FCM as normalization of Hgb and mean corpuscular volume measurements (based on patient age), along with a serum ferritin level ≥15 ng/mL. A partial response was defined as an increment of ≥1.0 g/dL in Hgb above preinfusion values for those children who did not meet the criteria for a complete response. When multiple values were present in the 4- to 12-week window, the laboratory value that showed the greatest increment in Hgb was chosen for the analysis.

Results

Seventy-two patients with IDA refractory to oral iron therapy (median age, 13.7 years; range, 9 months to 18 years) were treated with a total of 116 infusions of FCM (median dose, 750 mg; range, 132-750 mg) during the study period. Thirty-six patients (50%) received 2 doses, and 33 (46%) received 1 dose. The remaining 3 patients required 3 or 4 FCM infusions owing to ongoing blood loss. The median calculated iron deficit was 435 mg, and a median of 110% of the calculated iron deficit was administered. The study cohort was 68% female and 49% Latino (**Table I**). IDA due to heavy menstrual bleeding was the primary indication for FCM treatment in 41% of the patients (median age, 15.5 years), followed by gastrointestinal disorders in 32% (median age, 12.1 years), and nutritional IDA in 26% (median age, 2.1 years). All patients had previously been prescribed oral iron therapy for a median of 4 months (IQR, 2-12 months) yet exhibited limited or no increase above their baseline Hgb concentration. Adherence data were not collected.

Fifty-three patients had follow-up laboratory testing at 4-12 weeks after their FCM infusion(s) and were analyzed for response (**Table II**). All but 1 of these patients had a complete or partial hematologic response, including 36 children (68%) with a complete response (normalization of all postinfusion laboratory measurements) and 16 others (30%) with a partial response. The median preinfusion Hgb concentration was 9.4 g/dL in patients with a complete response, compared with

Table I. Characteristics of patients with IDA receiving FCM (n = 72)

Characteristics	%
Sex	
Female	68
Race/ethnicity	
Caucasian/White (Latino)	49
Caucasian/White (non-Latino)	22
African American/black	21
Asian/Indian	4
Native American	1
Multiracial	3
Age	
<2 y	17
2-5 y	14
5-12 y	8
12-18 y	61
Primary indication for FCM	
Heavy menstrual bleeding	41
No evidence of bleeding disorder	31
Underlying bleeding disorder*	10
Nutritional IDA	26
Breastfeeding without supplementation	3
Excessive cow's milk intake	19
Other low-iron diet	4
Gastrointestinal	32
Inflammatory bowel disease	12
Other gastrointestinal blood loss	17
Other malabsorption	3
IDA, etiology undetermined	1

*Bleeding disorder (von Willebrand disease, coagulation factor deficiency, or thrombocytopenia).