CLINICAL RESEARCH STUDY

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Iron Supplementation, Response in Iron-Deficiency Anemia: Analysis of Five Trials

Maureen M. Okam, MD, MPH,[a] Todd A. Koch,[b] Minh-Ha Tran, DO[c]

[a]Division of Hematology, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass; [b]Luitpold Pharmaceuticals, Inc, Norristown, Penn; [c]Departments of Pathology and Internal Medicine, University of California, Irvine School of Medicine.

ABSTRACT

BACKGROUND: Oral iron-replacement therapy is the mainstay of treatment for iron-deficiency anemia, but it is often poorly tolerated or ineffective. Hemoglobin response at day 14 of oral iron may be useful in assessing whether and when to transition patients from oral to intravenous (IV) iron.

METHODS: Pooled data from 5 randomized trials were analyzed to compare oral and IV iron-replacement therapy for iron-deficiency anemia. Treatment criteria and assignment to oral versus IV iron were defined per protocol; this analysis included only subjects receiving oral iron. Responders were subjects with ≥1.0-g/dL increases in hemoglobin at day 14, and nonresponders were those with smaller increases. Demographic and clinical characteristics were evaluated for association with hemoglobin response at multiple timepoints.

RESULTS: Most subjects (72.8%) were classified as responders. The proportion of subjects with hemoglobin increases ≥1.0, ≥2.0, and ≥3.0 g/dL was greatest among those with postpartum anemia, intermediate among those with heavy uterine bleeding or gastrointestinal-related causes of anemia, and lowest among those with other causes; this proportion was also significantly greater among responders than nonresponders. A ≥1.0-g/dL increase in hemoglobin on day 14 most accurately predicted satisfactory overall hemoglobin response to oral iron on day 42/56 (sensitivity 90.1%; specificity 79.3%; positive and negative predictive values of 92.9% and 72.7%, respectively). Iron-replacement therapy improved quality of life and reduced fatigue.

CONCLUSION: Hemoglobin responses <1.0 g/dL at day 14 of oral iron identify subjects with iron-deficiency anemia who should be transitioned to IV iron supplementation.

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KEYWORDS: Fatigue; Hemoglobin; Iron-deficiency anemia; Iron replacement therapy; Oral-to-IV transition; Quality of life

Iron is critical to a variety of physiologic processes, including respiration, energy production, and cell proliferation.[1] Iron deficiency is a condition in which the iron availability is insufficient to meet the body's needs; it can be present with or without anemia.[2-4] The 2013 Global Burden of Diseases, Injuries and Risk Factors study reported that the most common cause of anemia worldwide was iron deficiency, with the prevalence of other causes of anemia varying widely by geography, age, and gender.[5,6] Iron-deficiency anemia is associated with weakness, fatigue, difficulty concentrating, and reduced physical activity, which lead to impairment in quality of life and work productivity.[7-10] Alongside global public health recognition of the prevalence of iron-deficiency anemia, diagnosis and treatment require an astute clinician, a series of laboratory assays and other testing as indicated, a tolerable treatment regimen, and follow-up assessments of treatment response.[11-13]

The frontline of treatment for iron-deficiency anemia is oral iron replacement therapy, which is convenient, inexpensive,

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Requests for reprints should be addressed to Maureen M. Okam, MD, MPH, Hematology Division, Brigham and Women's Hospital, 75 Francis Street, Mid Campus 3, Boston, MA 02115.

E-mail address: mokam@bwh.harvard.edu

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and effective in the treatment of stable patients.[7,14-16] Although hemoglobin levels usually respond rapidly to oral iron therapy, repletion of iron stores and normalization of serum ferritin levels may require 3-6 months of treatment.[7] Long-term treatment with oral iron may be limited by intolerance associated with change of taste and gastrointestinal symptoms of nausea, vomiting, constipation, and abdominal discomfort.[7,16] In a meta-analysis comparing oral and intravenous (IV) iron supplementation, gastrointestinal adverse events were reported in 32% of subjects receiving oral iron compared with 13% receiving IV iron.[17] The poor tolerability may compromise adherence to oral iron therapy and, in turn, lead to persistence of iron-deficiency anemia.[14]

This secondary analysis of trial data was conducted to expand on the findings of a brief report showing that day-14 hemoglobin response to oral iron therapy may be a useful tool for clinicians in determining whether and when to transition patients from oral to IV iron.[18] Pooled data from 5 randomized trials were analyzed for the effect of oral iron therapy on hemoglobin response and quality of life in patients with iron-deficiency anemia stratified by cause.[19-23] The objective of this analysis was to identify a practical and sensitive predictor of response to oral iron replacement therapy that would be useful in clinical practice to inform decisions about transitioning from oral to IV iron therapy. A preliminary report of these data has been published as a letter to the editor.[18]

CLINICAL SIGNIFICANCE

- Patients with iron-deficiency anemia who did not respond adequately to oral iron therapy could be identified within 2 weeks of treatment initiation.
- A ≥1.0-g/dL hemoglobin increase after 2 weeks of oral iron therapy was an accurate predictor of subsequent hemoglobin responses at 6-8 weeks.
- Patients with a hemoglobin response <1.0 g/dL at week 2 of oral iron therapy should be considered for transition to intravenous iron supplementation.

METHODS

Data Sources

Datasets were pooled from 5 open-label, multicenter, randomized, controlled trials published 2007 to 2012 (**Table 1**).[19-23] Data were obtained from subjects allocated to oral iron therapy, and change from baseline in 5 hematologic parameters was measured on days 7, 14, 28, 42, and 56 (when available).[19-23] The hematologic parameters were hemoglobin, serum ferritin levels, transferrin saturation (TSAT), and percent and absolute reticulocyte counts. Subjects were categorized for causes of iron-deficiency anemia as postpartum anemia (3 studies),[19,20,22] heavy uterine bleeding (2 studies),[21,22] gastrointestinal (2 studies),[22,23] and other (1 study [multiple-dose]).[22]

Study Definitions

Subjects were classified as treatment responders if the hemoglobin increase from baseline to day 14 was ≥1.0 g/dL and as nonresponders if the increase was <1.0 g/dL. An overall satisfactory hemoglobin response was defined as a ≥2.0-g/dL increase from baseline to day 42 (day 56 in 1 study[23]). The diagnostic test utility for the 4 other hematologic measures was evaluated on the basis of specificity, sensitivity, positive predictive value, and negative predictive value associated with a ≥2.0-g/dL increase in hemoglobin at day 42 or 56. For this analysis the median change from baseline was used as the delineator between a positive and negative test result.

Subject-Reported Outcomes

Three trials measured changes in functional health status using the Medical Outcomes Study Short Form 36 (SF-36) instrument, version 2 (set of generic, coherent, and easily administered quality-of-life measures; higher scores = less disability).[19-21,23,24] Two trials assessed change in self-reported fatigue; one trial used the Fatigue Severity Scale, and the other trial used the Fatigue Linear Analog Scale Assessment.[19,21] The change from baseline scores in these self-administered assessment tools was evaluated at days 14, 28, and 42/56.

Data Analysis

All analyses were performed using data from the modified intent-to-treat population, defined as subjects who received ≥1 dose of randomized study medication and had ≥1 post-baseline hemoglobin assessment. Subjects with chronic kidney disease in the study by Barish et al[22] were excluded from the present analysis because of widespread acceptance of IV iron as first-line therapy in this population. Baseline and outcome data at days 14 and 28 and in the interval between days 42 and 56 were evaluated using Fisher's exact test for categoric variables and 1-way analysis of variance for continuous values. Sensitivity, specificity, and predictive values were calculated using online tools provided by GraphPad Software Inc (La Jolla, CA; www.graphpad.com). All statistical tests were performed post hoc, with no adjustment for type I error for multiple comparisons.

RESULTS

From the pooled data, 738 subjects who received oral iron were eligible for inclusion in this post hoc analysis. The pooled population had a mean age of 34.8 years (range, 15.3-80.0 years); the majority (96.2%) of subjects were women (**Table 2**). At baseline the median serum iron level was 27.0 μg/dL, the median hemoglobin level was 9.4 g/dL, and the median ferritin level was 9.1 ng/mL. The majority of subjects (537 of 738; 72.8%) achieved increases from baseline in hemoglobin ≥1.0 g/dL after 14 days of oral

Table 1 Summary of 5 Randomized, Controlled Trials with Assignment to Oral Iron Versus Intravenous Ferric Carboxymaltose for the Treatment of Iron-Deficiency Anemia

Study	Van Wyck et al, 2007[19]	Seid et al, 2008[20]	Van Wyck et al, 2009[21]	Barish et al, 2012[22]	Kulnigg et al, 2008[23]
Cause of iron-deficiency anemia	Postpartum anemia (N = 361)	Postpartum anemia (N = 291)	Heavy uterine bleeding (N = 477)	Various etiologies (N = 708)	Inflammatory bowel disease (N = 200)
Key inclusion criteria	Hb ≤10 g/dL (TSAT <50% or ferritin <500 ng/mL)	Hb ≤10 g/dL	Hb ≤11 g/dL, TSAT ≤25%, and ferritin ≤100 ng/mL	Hb ≤11 g/dL and ferritin ≤100 ng/mL (≤300 ng/mL if TSAT ≤30%)	Hb ≤10 g/dL and TSAT <20% or ferritin <100 ng/mL
Oral iron regimen	Ferrous sulfate 325 mg TID × 42 d	Ferrous sulfate 325 mg TID × 42 d	Ferrous sulfate 325 mg TID × 42 d	Standard of care: oral iron 42 d in multidose study	Ferrous sulfate (100 mg elemental iron) BID for 12 wk
Treatment compliance (%)	83.9	96.2	90.3	NA	98.5

BID = twice daily; Hb = hemoglobin; NA = not applicable; TID = three times daily; TSAT = transferrin saturation.

iron therapy and were classified as responders (Table 2). The remaining 201 subjects (27.2%) had changes from baseline in hemoglobin <1.0 g/dL at day 14 of oral iron therapy and were classified as nonresponders. Responders were significantly younger and had significantly lower body mass index and baseline hemoglobin level (all P <.001); baseline serum iron levels were also lower in responders than in nonresponders, although this difference did not reach statistical significance (P = .048). Other demographic and baseline clinical parameters did not differ significantly between responders and nonresponders.

In the overall pooled study population, the proportion of subjects achieving ≥1.0, ≥2.0, and ≥3.0 g/dL increases from baseline in hemoglobin level improved from day 14 to 28 and then increased more gradually through day 42/56 (Figure 1). At the final assessment, 88.6% of subjects overall (654 of 738) had ≥1.0-g/dL increases, 72.2% (533 of 738) had ≥2.0-g/dL increases, and 43.2% (319 of 738) had ≥3.0-g/dL increases in hemoglobin levels. When stratified by cause of anemia, the postpartum anemia group had the greatest percentage of subjects achieving ≥1.0-g/dL increases in hemoglobin at day 14 (95.5% [319 of 334]), followed by the groups with heavy uterine bleeding (56.3% [156 of 277]) and gastrointestinal-related (53.5%) and other causes (42.9% [24 of 56]) (Figure 2). These trends calculated by cause of anemia were also evident at the other time points assessed and when increases of ≥2.0 and ≥3.0 g/dL were used to define hemoglobin response.

Hemoglobin responses at day 28, day 42/56, and the final visit were evaluated according to response at day 14 of oral iron supplementation (Figure 3). Responders at day 14 had higher rates of hemoglobin response at day 28, day 42/56, and the final visit compared with nonresponders. All responders maintained ≥1.0-g/dL increases in hemoglobin at days 28 and 42/56, whereas 46.8% (94 of 201) and 63.2% (127 of 201) of nonresponders achieved ≥1.0-g/dL increases at days 28 and 42/56, respectively (both P <.0001 vs responders; Figure 3). Responders also had significantly higher rates of hemoglobin increases ≥2.0 g/dL compared with nonresponders, with 92.9% of responders (499 of 537) achieving hemoglobin increases ≥2.0 g/dL at day 42/56 compared with 27.4% of nonresponders (55 of 201) (P <.0001).

The ability of other clinical laboratory parameters (serum ferritin levels, TSAT, and reticulocyte counts) to predict a ≥2.0-g/dL increase in hemoglobin at day 42/56 after 7 or 14 days of oral iron treatment was evaluated by calculating the sensitivity, specificity, and positive and negative predictive values for each test (Table 3). A ≥1.0-g/dL increase in hemoglobin at day 14 (ie, responders) had a 90.1% sensitivity, 79.3% specificity, 92.9% positive predictive value, and 72.7% negative predictive value to predict a ≥2.0-g/dL increase in hemoglobin at day 42/56. The hemoglobin response ≥1.0 g/dL at day 14 was a better predictor of hemoglobin response ≥2.0 g/dL at day 42/56 than were responses in serum ferritin level, TSAT, or reticulocyte counts (Table 3).

Table 2 Demographic and Baseline Characteristics of 738 Study Subjects Assigned to Receipt of Oral Iron, Categorized by Day-14 Treatment Response of Change from Baseline Hemoglobin (Modified Intent-to-Treat Population)

Characteristic	Overall (N = 738)	Nonresponder (<1.0 g/dL) (n = 201)	Responder (≥1.0 g/dL) (n = 537)	*P* Value
Demographic characteristics				
Sex, n (%)				
Female	710 (96.2)	191 (95.0)	519 (96.6)	
Race				.931
Asian	99 (13.4)	4 (2.0)	95 (17.7)	
Black	219 (29.7)	97 (48.3)	122 (22.7)	
White	263 (35.6)	71 (35.3)	192 (35.8)	
Hispanic	149 (20.2)	27 (13.4)	122 (22.7)	
Other	8 (1.1)	2 (1.0)	6 (1.1)	
Age (y)				<.001
Mean (SD)	34.8 (12.2)	39.7 (12.7)	32.9 (11.5)	
BMI (kg/m^2)				<.001
Mean (SD)	28.7 (7.65)	31.1 (8.45)	27.9 (7.15)	
Baseline laboratory measures				
Hemoglobin (g/dL)				<.001
Mean (SD)	9.3 (1.2)	9.8 (1.1)	9.1 (1.1)	
Transferrin saturation (%)				.746
N	651	180	471	
Mean (SD)	8.3 (5.0)	8.2 (5.6)	8.3 (4.7)	
Ferritin (ng/mL)				
N	708	201	507	.099
Mean (SD)	16.8 (25.3)	14.3 (35.2)	17.8 (20.0)	
Total iron-binding capacity (μg/dL)				.280
N	682	181	501	
Mean (SD)	394.1 (72.4)	389.1 (57.5)	395.9 (77.0)	
Serum iron (μg/dL)				.048
N	738	201	537	
Mean (SD)	31.7 (21.7)	34.3 (28.2)	30.7 (18.5)	

BMI = body mass index; SD = standard deviation.

Changes in quality-of-life measures in response to oral iron are summarized in Table 4. Baseline total scores for the SF-36 were higher for subjects with anemia due to inflammatory bowel disease compared with subjects with anemia due to heavy uterine bleeding or who had postpartum anemia (Table 4). Treatment with oral iron improved quality of life and reduced fatigue as measured by the total score on the SF-36 scale, Fatigue Severity Score, and Fatigue Linear Analog Scale. Changes from baseline in the total score on the SF-36 scale were greatest in subjects with postpartum anemia and lowest in subjects with anemia due to gastrointestinal disease at all time points measured (Table 4). Improvements were greater the longer subjects remained on therapy (Table 4).

DISCUSSION

Oral iron therapy increased hemoglobin levels, with near-maximal response rates achieved by day 28. When stratified by cause of anemia, subjects with postpartum anemia had the highest hemoglobin response rates and were the most likely to achieve and sustain hemoglobin increases ≥2.0 g/dL. Subjects with heavy uterine bleeding and gastrointestinal-related causes of anemia had comparable but intermediate response rates, whereas those with other causes of iron-deficiency anemia had the lowest rates of response to oral iron supplementation. Overall, 90.1% of subjects with postpartum anemia, 49.3% with gastrointestinal causes of anemia, 45.8% with heavy uterine bleeding, and 35.7% with other causes had hemoglobin increases ≥2.0 g/dL at day 28. Further increases in response rates over time were small. From a clinical perspective, it would be ideal to identify at an early stage those subjects who would benefit from oral iron supplementation and who should be transitioned to IV iron therapy.

Subjects with hemoglobin increases <1.0 g/dL at day 14 (nonresponders) differed significantly from those who had increases ≥1.0 g/dL (responders) with respect to overall hemoglobin response by day 42/56 and the final visit. Notably, the nonresponders identified at day 14 were less likely to have significant increases in hemoglobin (≥2.0 g/dL) with continued oral iron therapy compared with the responders at day 14. We evaluated whether the hemoglobin response at day 14 or other early responses in serum ferritin

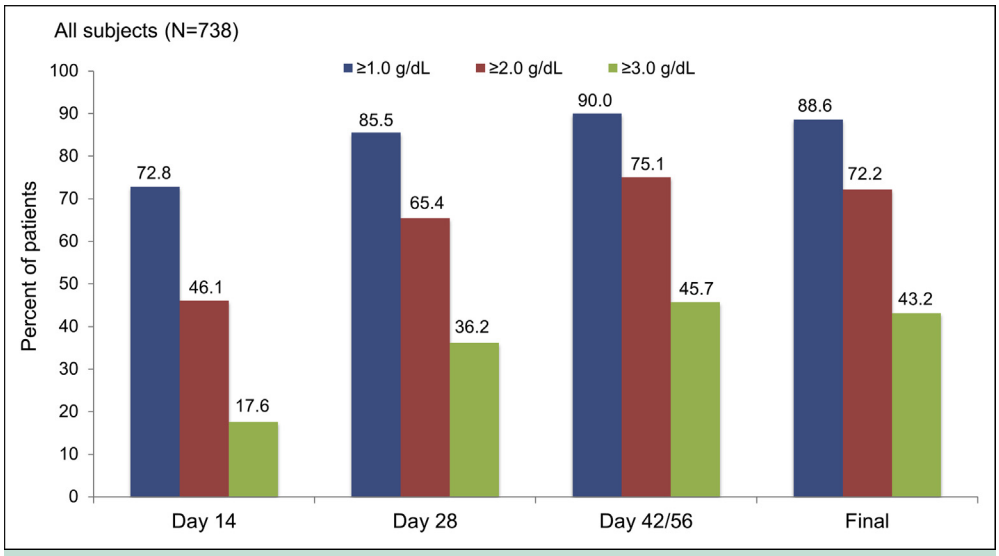

Figure 1 Hemoglobin response rate of the overall population in response to oral iron by time period.

levels, TSAT, and reticulocyte counts could predict the subsequent overall hemoglobin response with continued oral iron supplementation. An increase from baseline in hemoglobin values ≥1.0 g/dL at day 14 was identified as an accurate predictor of a ≥2.0-g/dL increase from baseline in hemoglobin at day 42/56 with continued oral iron, with a sensitivity of 90.1%, specificity of 79.3%, positive predictive value of 92.9%, and negative predictive value of 72.7%. An increase in hemoglobin values above the median of 1.1 g/dL at day 7 had higher specificity and positive predictive value but much lower sensitivity and negative predictive value. Responses based on the other clinical parameters (serum ferritin levels, TSAT, and reticulocyte counts) did not have acceptable sensitivity or specificity.

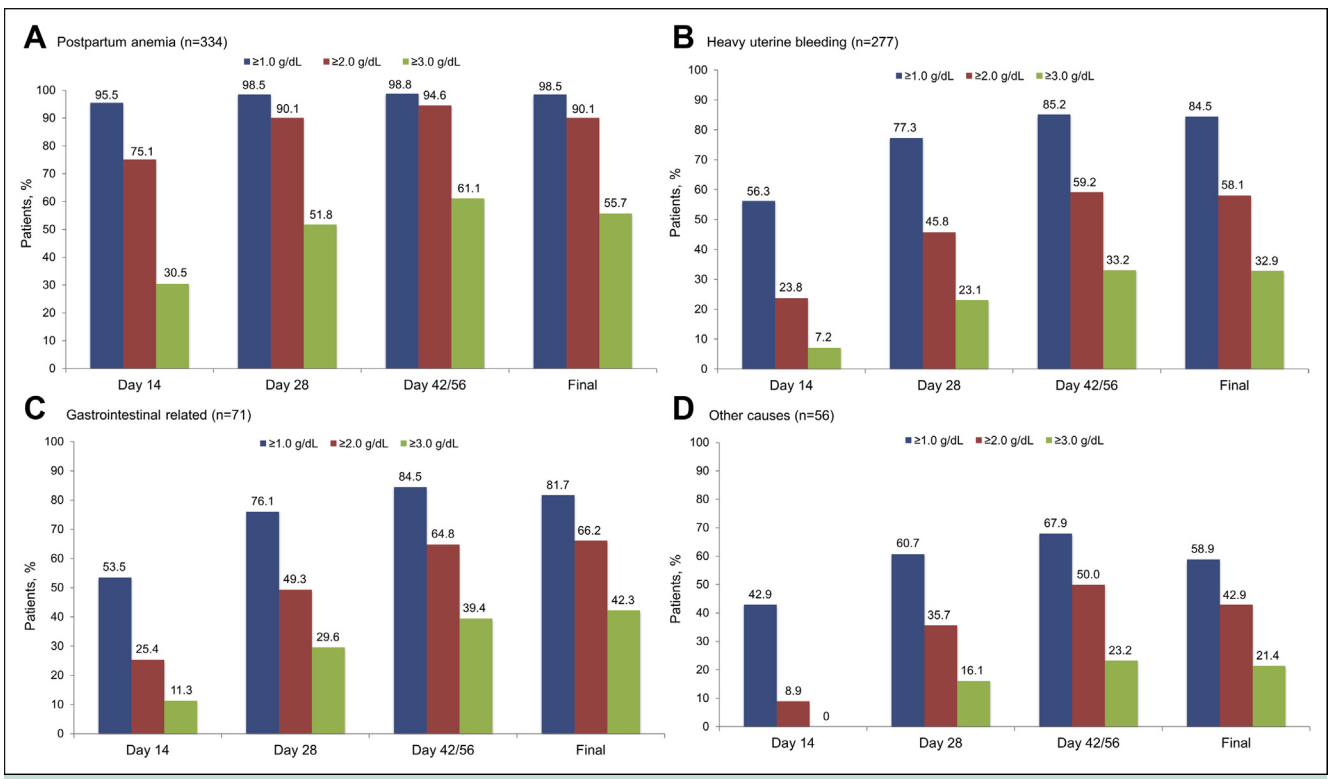

Figure 2 Hemoglobin responses to oral iron supplementation by time point and cause of iron-deficiency anemia: (**A**) postpartum anemia, (**B**) heavy uterine bleeding, (**C**) gastrointestinal-related causes, and (**D**) other causes.

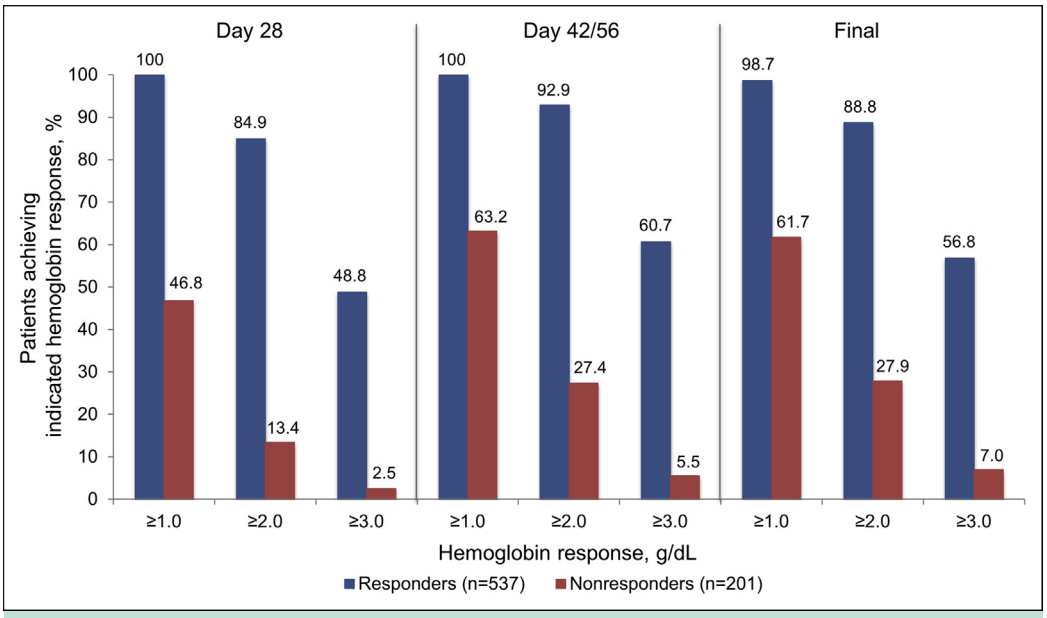

Figure 3 Hemoglobin responses by time point based on day 14 response. Responders had hemoglobin increases ≥1.0 g/dL and nonresponders had hemoglobin increases <1.0 g/dL after 14 days of oral iron supplementation.

Findings of the present analysis showed that subjects with iron-deficiency anemia who have hemoglobin increases <1.0 g/dL at day 14 of oral iron supplementation should be transitioned to IV iron. Similar findings were reported in a study conducted by Onken et al,[25] in which subjects with an increase in hemoglobin <1.0 g/dL after 14 days of oral iron treatment were randomly assigned to receive IV iron or continued oral iron treatment for 14 additional days. Mean hemoglobin increases were nearly 2 times greater in the IV iron group compared with the oral iron group ($P = .001$).

Iron deficiency, which often results in iron-deficiency anemia, is associated with fatigue, impaired quality of life, and decreased work capacity.[8-10] Baseline SF-36 scores for subjects with anemia due to inflammatory bowel disease in the present study (99.5 for the oral iron group; 97.5 for the IV iron group) were much higher than scores reported in 21 subjects with inflammatory bowel disease who had been anemic (51.4).[26] Administration of oral iron therapy to subjects with inflammatory bowel disease in the study by Wells et al[26] resulted in an increase of 15.0 points in the SF-36, a greater increase than observed in the present study. Iron therapy improved quality of life as measured by the SF-36 total score and reduced fatigue as measured by the Fatigue Severity Scale and the Fatigue Linear Analog Scale in the randomized clinical trials included in the present analysis. In a study conducted in Japanese premenopausal

Table 3 Assessment of Diagnostic Utility of Laboratory Measures as Early Predictors of >2-g/dL Increase at the Day 42-56 Interval

Laboratory Measure	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Day 7 after assignment to oral iron treatment				
Hemoglobin ≥1.1-g/dL increase*	64.8	91.4	95.9	45.3
Ferritin ≥4.9-μg/L increase*	48.6	42.0	72.3	20.8
TSAT ≥9.0% increase*	54.0	61.7	81.3	60.3
Reticulocyte count (absolute) ≥0.035 × 10^{12} increase*	55.5	63.4	81.9	32.3
Reticulocyte count (percent) ≥0.5% increase*	53.5	50.3	76.6	26.3
Day 14 after assignment to oral iron treatment				
Hemoglobin ≥1.0-g/dL increase	90.1	79.3	92.9	72.7
Ferritin ≥6.7-μg/L increase*	52.8	57.3	79.8	27.5
TSAT ≥10.0% increase*	56.0	62.9	82.9	30.9
Reticulocyte count (absolute) ≥0.026 × 10^{12} increase*	53.3	57.7	79.4	28.7
Reticulocyte count (percent) ≥0.3% increase*	46.7	39.9	70.8	19.4

NPV = negative predictive value; PPV = positive predictive value; TSAT = transferrin saturation.
*Median value for change from baseline.

Table 4 Assessment of Functional Health, Quality of Life, and Fatigue as Reported by Study Subjects Assigned to Oral Iron for the Treatment of Iron-Deficiency Anemia

Measure and Study Population	Baseline	Change: Baseline to Day 14	Change: Baseline to Day 28	Change: Baseline to Day 42/56
Fatigue, mean (95% CI)				
Postpartum anemia	n = 138	n = 137	n = 136	n = 136
(Fatigue Severity Scale)[20]	41.0 (39.2, 42.8)	−8.4 (−10.3, −6.5)	−11.1 (−13.2, −9.0)	-14.1 (−16.4, −11.8)
Heavy uterine bleeding	n = 220	n = 208	n = 208	n = 211
(Fatigue Linear Analog Scale)[21]	58.4 (55.1, 61.7)	−16.8 (−19.9, −13.6)	−24.0 (−27.5, −20.5)	−29.7 (−33.4, −25.9)
SF-36 scores, mean (SD)				
Postpartum anemia, mean (SD)[19]				
Total score	n = 163	n = 153	n = 152	n = 158
	58.2 (16.92)	10.2 (13.50)	16.1 (17.11)	20.9 (17.43)
Vitality	n = 162	n = 152	n = 151	n = 157
	41.4 (21.63)	12.6 (17.97)	18.2 (22.01)	26.3 (22.65)
Physical functioning	n = 162	n = 152	n = 151	n = 157
	61.3 (29.58)	16.0 (25.12)	22.1 (27.09)	26.5 (28.25)
Role physical	n = 162	n = 152	n = 151	n = 156
	48.8 (28.75)	12.2 (27.95)	23.4 (30.41)	30.3 (30.61)
Heavy uterine bleeding, mean (SD)[21]				
Total score	n = 224	n = 216	n = 216	n = 216
	62.8 (19.31)	7.3 (11.55)	10.7 (14.07)	12.3 (16.30)
Vitality	n = 224	n = 216	n = 216	n = 216
	39.0 (22.89)	15.7 (19.28)	20.9 (21.09)	24.0 (22.98)
Physical functioning	n = 224	n = 216	n = 216	n = 216
	68.0 (27.61)	4.6 (19.07)	10.6 (22.32)	11.0 (23.65)
Role physical	n = 224	n = 216	n = 216	n = 216
	67.2 (28.58)	4.6 (20.09)	9.3 (23.53)	11.6 (24.10)
Inflammatory bowel disease, mean (SD)[23]				
Total score	n = 21	NA	n = 20	n = 18
	99.5 (16.6)		0.7 (9.9)	5.6 (14.5)
Vitality	n = 21	NA	n = 20	n = 18
	14.24 (3.58)		−0.03 (2.66)	1.44 (3.15)
Physical functioning	n = 21	NA	n = 20	n = 18
	24.76 (3.52)		0.02 (1.79)	0.53 (2.35)
Role physical	n = 21	NA	n = 20	n = 18
	6.19 (1.70)		−0.13 (1.24)	0.17 (1.89)

CI = confidence interval; SD = standard deviation; SF-36 = Medical Outcomes Study Short Form 36 instrument, version 2.

women diagnosed with iron-deficiency anemia, baseline vitality and general health scores as measured by the SF-36 were significantly lower than Japanese norms.[27] Treatment with oral iron supplementation resulted in significant increases from baseline in all subscales of the SF-36 except the subscale that evaluated emotional role functioning. Furthermore, treatment of iron-deficiency anemia was previously shown to improve quality of life in subjects with Crohn's disease and chronic heart failure.[28,29]

Intravenous iron is more effective than oral iron in producing sustained hemoglobin responses and reducing the need for blood transfusions.[30] Newer formulations of IV iron allow administration of larger individual doses, which may be beneficial in clinical use. In a meta-analysis of 103 trials published from 1966 through 2013, IV iron was not associated with an increased risk of severe adverse events compared with control treatments (ie, oral iron, intramuscular iron, placebo, or no iron): the relative risk (RR) was 1.04 (95% confidence interval [CI], 0.93-1.17).[31] The risk of serious infusion reactions was increased with IV iron (RR 2.47; 95% CI, 1.43-4.28), particularly with ferric gluconate (RR 5.32; 95% CI, 1.49-18.99), but other iron formulations were not associated with significantly increased risk. Additionally, the risk of serious infection was not increased by IV iron (RR 0.96; 95% CI, 0.63-1.46). These findings provide reassurance of the safety of IV iron, making it a viable alternative for patients who do not respond well to oral iron therapy.

Several limitations should be noted in the present study. Although the potential bias of the individual randomized, controlled trials was evaluated, there remains inherent bias due to the post hoc design of the present analysis that uses pooled data from several studies. In addition, the multiple comparisons create the chance of a type 1 error ("false positive") in the conclusions. In addition, the high level of compliance with the use of oral iron observed in the present

studies ranged from 83.9% to 98.5% and may be higher than what is typically observed in the real-world setting, contributing to the limitations.

In this analysis of subjects with iron-deficiency anemia receiving oral iron therapy, those who responded achieved increases in hemoglobin and experienced improvements in quality of life. The hemoglobin response to oral iron therapy varies with the causes of anemia and subject characteristics. A hemoglobin increase $\geq$1.0 g/dL from baseline at day 14 of oral iron is an accurate predictor of the subsequent overall hemoglobin response with continued oral supplementation. In clinical practice, nonresponders (ie, hemoglobin increase $<$1.0 g/dL at day 14) should be transitioned to IV iron supplementation.

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