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Changes in Hepcidin and Hemoglobin After anti-TNF-alpha Therapy in Children and Adolescents with Crohn's Disease

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Abstract

Background—Anemia is the most common systemic complication of inflammatory bowel disease, is more common in affected children than adults, and is mediated in large part by chronic inflammation. Inflammation increases levels of the iron-regulatory protein hepcidin, which have been elevated in adults with Crohn's disease.

Methods—We measured serum hepcidin-25 and hemoglobin (Hgb) in 40 children and adolescents with Crohn's disease at baseline and 10 weeks after initiation of anti-TNF-α therapy. Measures of disease activity, inflammatory markers, and cytokines were obtained in all subjects. Anemia was defined by World Health Organization criteria.

Results—At baseline hepcidin and C-reactive protein (CRP) levels were correlated, and 95% of subjects were anemic. After anti-TNF- α therapy, median (IQR) hepcidin concentrations

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Meredith A. Atkinson made a substantial contribution to the design of this work and to the analysis and interpretation of the data, drafted the work, had final approval of the manuscript, and agrees to be accountable for all aspects of the work.

Mary B. Leonard substantially contributed to the conception and design of this work and to the acquisition, analysis, and interpretation of the data, critically revised the work for important intellectual content, had final approval of the manuscript, and agrees to be accountable for all aspects of the work.

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decreased significantly and the distribution narrowed (27.9 [16.2, 52.9] vs. 23.2 [11.1, 37.7] ng/mL, p=0.01). Mean (SD) Hgb also increased significantly (10.6 ± 1.2 to 10.9 ± 1.1 g/dL, p=0.02), and the increase was sustained at 12 months, although 90% of participants continued to meet anemia criteria at 10 weeks. Disease activity and markers of inflammation also decreased and albumin levels increased. In generalized estimating equation analyses, higher TNF-α, IL-6, ESR and CRP were associated with higher hepcidin concentrations (p=0.04, p=0.03, p=0.003, and p<0.001 respectively), and increased levels of disease activity were associated with higher hepcidin.

Conclusions—In children with Crohn's disease, anti-TNF-α therapy is associated with decreased levels of hepcidin and increased Hgb 10 weeks after induction. Improvement in anemia may be a secondary benefit for children who receive this therapy.

Keywords

inflammatory bowel disease; anemia of inflammation; pediatric

INTRODUCTION

Anemia is the most common systemic complication of inflammatory bowel (IBD), with higher prevalence in children compared to adults.[1] In a recent cross-sectional study, the prevalence of anemia was 70% in children, 42% in adolescents and 40% in adults.[2] We reported a prevalence of 77% in children and adolescents with incident Crohn's disease.[3] Anemia is associated with decreased quality of life and cognitive function, and interventions to increase hemoglobin (Hgb) resulted in improved quality of life scores, independent of disease activity, in patients with IBD.[4–6]

The etiology of anemia in IBD is multifactorial but often due in part to inflammation; other contributing factors include iron/micronutrient deficiency, chronic blood loss in the gastrointestinal tract, and medication-induced myelosuppression.[7,8–10] Enteral iron supplementation is the mainstay of therapy for iron deficiency anemia but may be poorly tolerated and of limited efficacy in patients with malabsorption, while intravenous iron carries risk for anaphylactic reactions.[1,2] Treatment with erythropoiesis stimulating agents may be helpful in treating refractory anemia, but inflammation-mediated impaired iron trafficking often results in resistance to these agents.[1,5,11]

Chronic inflammation results in increased levels of the iron-regulatory protein hepcidin, contributing to anemia in patients with IBD. Hepcidin is encoded by the HAMP gene and produced in the liver. Hepcidin regulates intestinal iron absorption and body iron distribution through its post-translational suppression of cell membrane expression of ferroportin, the sole cellular iron exporter.[12] Regulation of hepcidin expression in the liver occurs at the transcriptional level, with the key modulators being iron status, hypoxia, and inflammation.[12] Hepcidin is initially synthesized as an 84 amino acid prepropeptide, which is then undergoes cleaved by the prohormone convertase furin to the active 25 amino acid form.[12–17] Hepcidin binding causes internalization and degradation of ferroportin, resulting in down-regulation of dietary iron absorption by intestinal enterocytes and inhibition of

stored iron release from reticulendothelial cells, preventing the utilization of absorbed or stored iron for erythropoiesis in the bone marrow.[13,15,18]

Prior studies demonstrated that serum levels of hepcidin were elevated in adults with Crohn's disease compared to healthy controls, and were positively correlated with disease activity and serum concentations of C-reactive protein (CRP) and IL-6.[7,19,20] Hepcidin levels were negatively correlated with Hgb levels in adults with IBD.[7,19,20] Clinial trials in adults with ankylosing spondylitis and rhematoid arthritis demonstrated that treatment with the TNF-α inhibitors results in decreases in hepcidin and improved Hgb.[21,22] However, these results may not be generalizable to patients with IBD, and no studies have examined changes in hepcidin levels and anemia parameters in patients with IBD.

This study takes advantage of stored serum specimens from a prospective cohort study conducted to examine changes in bone and mineral metabolism in children and adolescents following initiation of anti-TNF-α therapy.[23,24] We previously reported significant improvements in disease activity and decreases in cytokine levels over the first 10 weeks of therapy. The objectives of this study were to correlate hepcidin concentrations with the severity of anemia and markers of inflammation at baseline, and to describe changes in hepcidin levels and Hgb over time.

METHODS

Study Population

This analysis was performed as an ancillary study within a larger prospective cohort study of bone and mineral metabolism conducted in 90 children and adolescents with Crohn's disease recruited from the IBD clinic at the Children's Hospital of Philadelphia (CHOP), as previously described.[23,24] The baseline study visit was completed at the time of the first infliximab infusion. All participants underwent 6 weeks of infliximab induction therapy (dosed at baseline, 2 weeks, and 6 weeks) for treatment of refractory CD as prescribed by their gastroenterologist and a follow-up study visit was completed at 10 weeks. Forty particpants from the parent study with sufficient quantities of stored serum available for quantification of hepcidin at baseline and 10 weeks were included in this analysis. Thirty-seven subjects received 5 mg/kg infliximab at baseline with the additional 3 subjects receiving 6–7 mg/kg at baseline. Thirty-six subjects received 5 mg/kg for the second dose, 3 subjects 6–7 mg/kg, and 1 subject 9 mg/kg. Four subjects received 6–10 mg/kg for the third dose, with the remainder receiving 5 mg/kg.

CD was confirmed by endoscopic, histological, and clinical parameters, as previously described.[23,24] Disease activity was assessed at each study visit using the Pediatric Crohn's Disease Activity Index (PCDAI; score range 0–100).[25] Disease activity was categorized as none (1–10), mild (11–30), and moderate-to-severe (>30). Disease characteristics were obtained by questionnaire and confirmed in the medical record.

Study variables/Laboratory measurements

Serum TNF-α and IL-6 were measured by the Luminex platform and the human cytokine six-plex high-sensitivity anti-body bead kit (Millipore) with a sensitivity of 0.08 and 0.10 pg/mL and interassay variation of 8.3% and 7%, respectively.

Hgb was calculated as Hct multiplied by 0.3. Anemia was defined according to World Health Organization (WHO) criteria as Hgb < 11.5 g/dL in children aged 2–11 years, < 12 g/dL in females aged ≥ 12 years, < 13 g/dL in males 12 - < 18 years, and < 13.5 g/dL in males ≥ 18 years.[26] In addition to baseline and 10-week data, 36 participants had Hgb available from a 12-month follow up visit. Hepcidin-25, the biologically active form of the peptide, was measured using a validated competitive enzyme-linked immunosorbent assay (ELISA), with sensitivity of 5 ng/mL and interassay variability of 12%, in a single laboratory (Intrinsic LifeSciences, La Jolla, CA).[27]

Statistical Analysis

All analyses were performed using STATA 14.0 (Stata Corp., College Station, TX). A two-sided p value of <0.05 was considered statistically significant. Distributions of continuous variables were assessed for normality. For normally distributed data, mean ± SD was reported and changes between baseline and 10 weeks were assessed using the paired *t* test. For skewed data, median and IQR were reported and differences assessed using the Wilcoxon signed-rank test. Pearson chi2 testing was used for comparison of proportions. One-way analysis of variance was used to compare mean Hgb at baseline, 10-week, and 12-month follow-up. Univariate and multivariable generalized estimating equation (GEE) regression analyses were used to evaluate correlates of hepcidin at each visit including TNF-α, IL-6, ESR, CRP, PCDAI, and albumin. Skewed data were natural log-transformed for the GEE models.

ETHICAL CONSIDERATIONS

The Institutional Review Board at the University of Pennsylvania approved the study protocol. Informed consent was obtained from participants ≥ 18 years of age, and assent along with parental consent from subjects < 18 years, as appropriate.

RESULTS

Table 1 displays baseline demographic and clinical characteristics and Table 2 summarizes the baseline laboratory results. There were no significant differences in baseline age, Hgb, PCDAI, height, BMI Z-score, sex or race between subjects from the parent study with hepcidin measures vs. the 43 subjects under the age of 21 who did not have hepcidin measured. The median PCDAI score was 28; 48% had mild disease activity and 36% moderate-to-severe disease activity at baseline. Mean Hgb was 10.6 ± 1.2 g/dL and 95% of subjects were anemic at baseline. Serum CRP was positively correlated with hepcidin concentrations at baseline (r=0.34, p=0.03); no other covariates of interest were correlated with baseline hepcidin concentrations in univariate analyses.

Table 2 summarizes measures of disease activity, inflammation, and anemia at baseline and 10 weeks. Hepcidin concentrations decreased significantly and the distribution narrowed following the anti-TNF-α intervention (Figure 1a, Supplemental Digital Content). Mean Hgb also increased significantly (Figure 1b, Supplemental Digital Content), although 90% of participants were anemic at 10 weeks. The PCDAI and markers of inflammation decreased significantly and albumin levels increased significantly, as previously reported in the larger study.[23,24]

A subset of participants (36 of 40) had repeat Hgb measured at 12 months after induction. Mean (SD) Hgb values at baseline, 10 weeks, and 12 months respectively were 10.6 (1.2), 10.9 (1.1), and 11.1 (0.9) g/dL (p=0.09). In addition, the increase in Hgb noted at 10 weeks was sustained after 12 months of follow-up, with no significant difference between mean (SD) 10-week and 12-month Hgb levels – 11.0 (0.17) vs. 11.1 (0.15) g/dL, (p=0.64). (Figure 1b)

In a univariate GEE analysis, higher CRP ($p<0.001$), higher ESR, IL-6 and PCDAI ($p<0.01$), and higher TNF-α ($p=0.03$) were associated with higher hepcidin. Serum albumin was inversely associated with hepcidin ($p<0.001$). Hepcidin was not significantly associated with Hgb or anemia. In multivariate GEE analyses (Table 3), significant positive associations between hepcidin and TNF-α, IL-6, ESR and CRP persisted. A dose response was noted for PCDAI, with more severe disease activity associated with significantly higher hepcidin levels.

DISCUSSION

This is the first longitudinal study in an IBD cohort to report acute changes in serum hepcidin, inflammatory markers and Hgb after anti-TNF-α induction therapy with infliximab. The decrease in hepcidin levels, associated with a concurrent marked decrease in cytokines, inflammatory markers and CD activity, suggests that the potent anti-inflammatory actions of TNF-α blockade may to extend to suppression of the specific stimuli for hepcidin production. In addition to decreased hepcidin, we also noted a small but significant increase in Hgb over the study period, suggesting that anti-TNF-α treatment may contribute to increasing Hgb levels via interruption of the stimulatory effect of inflammation on hepcidin production. These findings suggest that stimuli for hepcidin transcription, which in turn contribute to iron-restricted erythropoiesis and anemia, are relieved after anti-TNF-α induction, supporting a link between hepcidin, abnormal iron homeostasis, inflammatory cytokines, and CD activity.

Previous observational studies have shown that hepcidin is elevated in adults with IBD, and our findings further demonstrate that hepcidin decreases in response to anti-TNF-α therapy.[7,19] Cross-sectionally, increased serum IL-6 and hepcidin levels are also negatively correlated with hemoglobin in IBD patients, and our results expand on this observation to suggest that TNF-α blockade has opposing effects on hepcidin and hemoglobin.[20] Our findings also build upon data from other inflammatory disease states. Patients with ankylosing spondylitis treated with infliximab demonstrate improvement in hemoglobin levels and decreased prevalence of anemia compared to those receiving placebo, and those

with higher baseline IL-6 or CRP were more likely to demonstrate improvement in hemoglobin.[21] In adults with rheumatoid arthritis, patients treated with either anti-IL-6 receptor antibody or infliximab demonstrated decreased hepcidin and improvements in anemia, with a notably lower anemia prevalence at baseline of 66% compared to 95% in our CD cohort.[22] The decrease in hepcidin was also more significant in rheumatoid arthritis patients treated with an anti-IL-6 receptor antibody compared to infliximab, suggesting that IL-6 may be a more potent stimulator of hepcidin production than TNF-α. However, our findings also suggest that the inflammatory marker most significantly negatively associated with hepcidin is low serum albumin. Inflammation leads to hypoalbuminemia by decreasing its rate of synthesis in the liver, increasing its fractional catabolic rate, and in some cases by increasing albumin transfer out of the intravascular compartment.[28] It has been shown that patients with active CD have lower serum albumin compared to those with inactive disease[29], and our findings demonstrated a significant increase in albumin after infliximab induction. In addition to albumin's role as a marker of nutrition, this suggests that hypoalbuminemia may be a more specific marker of type of the specific inflammatory stimulus for upregulating hepcidin production than levels of individual cytokines.

Clarification of the mechanisms regulating hepcidin production in IBD is critical toward developing interventions to inhibit hepcidin production, allowing us to move beyond our current anemia therapies. Although infliximab does not directly inhibit IL-6 activity, its association with decreased hepcidin levels may suggest that TNF-α inhibition indirectly reduces IL-6 production leading to down-regulation of hepcidin production. In a mouse model of colitis, treatment with the novel docosahexaenoic acid-derived resolving agent maresin 1 resulted in both decreased IL-6 and TNF-α concentrations and reduced expression of liver hepcidin mRNA, suggesting that broader, non-TNF-α-specific IBD therapies also have the potential to down-regulate hepcidin.[31] There is evidence that TNF-α may specifically contribute to apoptosis of erythroid precursors in the bone marrow, but whether via an iron- and hepcidin-independent mechanism is unclear.[30] In addition to anti-cytokine agents there are monoclonal antibodies, both against hepcidin and blocking its binding to ferroportin, in Phase I trials which may soon provide more targeted treatment options for hepcidin-mediated anemia in a variety of conditions.[12]

Although there was a statistically significant increase in Hgb after induction, nearly 90% of subjects remained anemic. This parallels the results of a recent study by Koutroubakis et al. in 430 adults with IBD in which no significant change in anemia prevalence (38.1% vs 36.6%) was observed one year after treatment with anti-TNF-α agents, despite a significant 0.2 g/dl increase in median Hgb at 1 year in 134 anemic subjects.[32] Potential reasons for persistently prevalent anemia despite anti-TNF-α therapy include ongoing inflammation- and iron-independent contributors to anemia. Patients with IBD may have absorption issues which decrease the effectiveness of enteral iron therapy. With the inflammatory stimuli of hepcidin production interrupted after induction therapy, consideration of IV iron therapy for management of anemia may be more efficacious given decreased iron sequestration compared to during the active phase of disease. The observed increase in Hgb seen at 10 weeks was also sustained 12 months after induction therapy.

The primary limitations of this retrospective, ancillary study are lack of markers of iron status (iron,ferritin) or data on iron supplementation, preventing assessment of iron-deficiency as a risk factor for anemia.. As the parent study was focused on bone and mineral metabolism in IBD, iron-specific data elements were not incorporated into the primary data collection. In addition, the uncontrolled nature of this study is a limitation. However, our observations are unlikely to be due to disease natural history, given the magnitude of changes over a relatively short duration of follow-up. There were no specific QOL assessments available to clarify whether the increase in hemoglobin seen at the follow up visits was clinically significant.

This study does have several strengths. The study of a targeted biological therapy in a single disease, uniformity of dosing, and consistent timing of short-term follow-up support a relationship between inflammation and hepcidin levels, and response of Hgb to this therapy.

In summary, our results suggest that treatment with infliximab is associated with improvement in Hgb levels, sustained over 12 months, which is associated with a significant decrease in hepcidin levels after induction therapy. These results should not be interpreted to suggest that TNF-α inhibition should be a primary treatment for the anemia associated with CD, but rather that improvement in Hgb may be a secondary benefit in children who are candidates for infliximab. In the future, targeted hepcidin antagonists may provide alternative therapies for the specific anemia of Crohn's disease/IBD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SUMMARY BOX

What is Known

- Anemia is a common complication in children with IBD
- The iron-regulatory protein hepcidin mediates the anemia of inflammation
- Adults with Crohn's disease have elevated hepcidin levels

What is New

- We demonstrated longitudinal decrease in hepcidin levels 10 weeks after infliximab induction therapy in a cohort of children and adolescents with Crohn's disease
- Decrease in hepcidin was associated with significantly increased hemoglobin in the cohort, and the increase was sustained 12 months after therapy
- Improvement in anemia management may be a secondary benefit in children who are candidates for infliximab

Table 1

Baseline clinical and demographic characteristics (n=40)

Characteristic	
Age (years), mean (SD)	13.9 (3.5)
Female, % (n)	34 (13)
Black race, % (n)	15 (6)
Height Z-score, mean (SD)	−0.40 (1.03)
BMI Z-score, mean (SD)	−0.02 (1.08)
PCDAI, mean (SD)	28 (15)
Site of Disease, % (n)	
Isolated upper gastrointestinal disease	80 (32)
Isolated ileal disease	5 (2)
Ileocolonic disease	78 (31)
Isolated colonic disease	18 (7)
Perianal disease	35 (14)

BMI, body mass index; PCDAI, Pediatric Crohn's disease activity index

Table 2

Measures of Anemia, Inflammation, and Disease Activity at Baseline and After Anti-TNF-α Induction Therapy (Presented as mean ± SD, median (IQR) or % [n])

Characteristic	Baseline	10 Weeks	p-value[a]
Hemoglobin, g/dL	10.6 ± 1.2	10.9 ± 1.1	0.02
Anemic, % (n)	95 (38)	89 (35)[α]	0.38
Hepcidin, ng/mL	27.9 (16.2, 52.9)	23.2 (11.1, 37.7)	0.01
CRP, mg/dL	1.2 (0.5, 2.7)	0.5 (0.3, 0.6)	<0.001
ESR, mm/hr	26 (12, 40)	10 (6, 15.5)	<0.001
IL-6, pg/mL	13.7 (6.3, 27.9)	5.6 (2.7, 15.1)	0.003
TNF-α, pg/mL	7.4 (4.9, 10.7)	1.9 (1.0, 3.7)	<0.001
PCDAI	30 (17.5, 40)	11 (7.5, 15)	<0.001
Albumin, g/dL	3.8 ± 0.6	4.1 ± 0.4	0.001

[a]Paired *t* test, Wilcoxon signed-rank test, or Pearson chi2 test as appropriate

[α]n=39, 1 subject missing hemoglobin at 10 weeks

Table 3

Multivariable Generalized Estimating Equation (GEE) Regression Analyses of the Association between Measures of Inflammation and Hepcidin Concentrations

Model[a]	% Difference in Hepcidin[b]	95% CI	P value
TNF-α per 10%	1.2	(0.1, 2.3)	0.04
IL-6 per 10%	1.8	(0.2, 3.5)	0.03
ESR per 1 mm/hr	1.6	(0.5, 2.7)	0.003
CRP per 1 mg/dl	18	(9.5, 27.1)	<0.001
PCDAI vs. 0–10 (No disease)			
10–30 (Mild)	48.3	(9.8, 100.2)	0.01
>30 (Moderate)	88.7	(14.7, 210.4)	0.01

[a]All models adjusted for age, sex and race. Each variable is expressed as a 10% difference for variables that are natural log-transformed, or a one unit difference for variables that are untransformed in the GEE model.

[b]Hepcidin was natural log-transformed in all models. The % difference was calculated as $(1.1^{\beta} - 1) \times 100$ for log-transformed variables and $(e^{\beta} - 1) \times 100$ for untransformed variables, where β is the regression parameter for the variable of interest.