Improvement of Health-Related Quality of Life in Children with Inflammatory Bowel Disease Receiving Routine Intravenous Iron Supplementation

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OBJECTIVES Iron deficiency anemia (IDA) is very common in children with inflammatory bowel disease (IBD). While health-related quality of life (HRQL) is a key outcome measure, no long-term studies have evaluated the effect of correction of IDA on HRQL in children with IBD. Our goal was to prospectively study changes in HRQL in iron-deficient children with IBD receiving routine iron supplementation with periodic intravenous iron sucrose (IVIS).

METHODS Thirty-eight children with IBD treated with infliximab participated. Hematology and inflammatory markers were assessed before each infliximab treatment. Iron-deficient patients (transferrin saturation below 20% and/or ferritin below 30 ng/mL or 100 ng/mL with normal or elevated C-reactive protein, respectively) received IVIS after each infliximab infusion until iron indices stayed normal for two consecutive measurements. HRQL was assessed with Pediatric Quality of Life Inventory every 4 months. Correlation between changes in mean hemoglobin levels and HRQL scores was analyzed prospectively in 3-month periods over a period exceeding 3 years.

RESULTS At enrollment, 27 patients had already been established on infliximab; 11 had not started or completed induction. Mean iron indices and hemoglobin normalized after 3 and 6 month of starting IVIS, respectively. Multiple HRQL parameters significantly improved, regardless of the duration of infliximab treatment at the time of enrollment. There was a statistically significant positive correlation between correction of anemia and improvement in parent-reported emotional and physical HRQL scores.

CONCLUSIONS Periodic IVIS resulted in long-term correction of IDA in children with IBD. Correction of IDA contributed to some improvements in HRQL.

ABBREVIATIONS CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, Hemoglobin; HRQL, Health-related quality of life; IBD, inflammatory bowel disease; IDA, iron deficiency anemia; IVIS, intravenous iron sucrose; PCDAI, Pediatric Crohn Disease Activity Index; PUCAI, Pediatric Ulcerative Colitis Activity Index; TSAT, transferrin saturation

KEYWORDS children; health-related quality of life; inflammatory bowel disease; iron deficiency anemia; iron sucrose

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Introduction

Anemia is one of the most common complications of inflammatory bowel disease (IBD).¹ The etiology is multifactorial, with iron deficiency being the main contributor.² Anemia and iron deficiency are more common in children than in adults with IBD, affecting up to 74% of patients.^{3,4} Iron deficiency anemia (IDA) has special significance in pediatric IBD due to its adverse effects on development and cognitive function from infancy to school age.^{5,6}

Health-related quality of life (HRQL) is a key outcome measure in clinical research.⁷ Anemia has been associated with poor HRQL in both children⁸ and adults⁹ with IBD. Findings in adults suggest that iron deficiency, even in the absence of anemia, may have deleterious

effects.¹⁰ This is not surprising given the essential role of iron-containing proteins and enzymes in oxygen delivery to tissues, energy metabolism, myelin synthesis, and neurotransmission.¹¹

Oral iron is the mainstay of routine supplementation in children with IBD, despite significant disadvantages, including poor adherence^{12,13} and poor absorption in the presence of inflammation.^{14,15} Intravenous iron sucrose (IVIS) has been shown to be superior to oral iron for correction of IDA¹⁶ and to improve HRQL in adults.^{9,17–20} There has been increasing interest in the use of intravenous iron in children with IBD, and several recent studies^{21–24} have demonstrated the safety and efficacy of IVIS. However, the effect of correction of IDA on HRQL in children with IBD has not been investigated.

Table 1. Summary of Baseline Demographic and Clinical Data

	Entire Cohort	Established IFX	New IFX
Sex, n (%)			
Male	22 (58)	16 (59)	6 (55)
Female	16 (42)	11 (41)	5 (45)
Age, yr, mean $\pm$ SD			
At diagnosis	11.0 $\pm$ 3.2	11.1 $\pm$ 2.9	10.7 $\pm$ 3.6
At enrollment	12.9 $\pm$ 3.3	13.5 $\pm$ 3.0	11.5 $\pm$ 3.7
Diagnosis, n (%)			
Crohn disease	33 (87)	25 (93)	8 (73)
Ulcerative colitis	5 (13)	2 (7)	3 (27)
Variables, mean $\pm$ SD			
Duration of IFX treatment (mo)	7.2 $\pm$ 10.9	9.2 $\pm$ 11.8	0.4 $\pm$ 0.2
Hemoglobin (mg/dL)	11.95 $\pm$ 1.51	12.5 $\pm$ 1.2 [†]	10.68 $\pm$ 1.6
Ferritin (ng/mL)	24.71 $\pm$ 18.32	28.2 $\pm$ 19.2	21.3 $\pm$ 20.3
Transferrin saturation (%)	14.95 $\pm$ 8.60	15.7 $\pm$ 6.8	12.0 $\pm$ 9.7
Albumin (g/dL)	3.45 $\pm$ 0.47	3.5 $\pm$ 0.5	3.6 $\pm$ 0.5
ESR (mm/hr)	12.16 $\pm$ 10.17	13.3 $\pm$ 11.5	10.0 $\pm$ 6.5
CRP*	89	81	100
PCDAI	16.4 $\pm$ 14.5	14.6 $\pm$ 14.6	20.9 $\pm$ 14.2
PUCAI	0.5 $\pm$ 1.1	2.5 $\pm$ 3.5	0
Patient-reported HRQL score			
Psychosocial	78.29 $\pm$ 14.65	77.81 $\pm$ 14.47	77.45 $\pm$ 14.88
Emotional	79.01 $\pm$ 20.16	79.90 $\pm$ 20.89	75.00 $\pm$ 18.71
Social	88.16 $\pm$ 13.73	88.08 $\pm$ 15.80	87.27 $\pm$ 11.91
School functioning	67.63 $\pm$ 17.07	65.38 $\pm$ 15.99	70.00 $\pm$ 17.75
Physical	78.79 $\pm$ 18.32	80.85 $\pm$ 15.80	72.82 $\pm$ 23.51
Total	78.42 $\pm$ 14.51	78.85 $\pm$ 13.22	75.73 $\pm$ 17.29
Parent-reported HRQL score			
Psychosocial	71.50 $\pm$ 16.51	71.42 $\pm$ 16.79	69.82 $\pm$ 16.10
Emotional	68.82 $\pm$ 19.19	71.54 $\pm$ 20.04 [†]	60.45 $\pm$ 14.70
Social	82.24 $\pm$ 19.75	82.69 $\pm$ 20.75	80.45 $\pm$ 18.90
School functioning	63.42 $\pm$ 20.31	60.19 $\pm$ 19.62	68.18 $\pm$ 20.28
Physical	74.63 $\pm$ 20.98	77.92 $\pm$ 19.49 [†]	66.54 $\pm$ 24.00
Total	72.38 $\pm$ 17.15	73.40 $\pm$ 16.93	68.64 $\pm$ 18.23

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HRQL, health-related quality of life; IFX, infliximab; PCDAI, Pediatric Crohn Disease Activity Index; PUCAI, Pediatric Ulcerative Colitis Activity Index

* Proportion of patients with normal CRP (%).

[†] $p < 0.05$ compared with new IFX group.

In this study, we have prospectively evaluated changes over 3 years in hematology, iron indices, and HRQL in pediatric IBD patients who received IVIS for routine iron supplementation. To our knowledge, this is the first study to analyze longitudinal changes in HRQL as a function of correction of IDA with intravenous iron in pediatric IBD.

Materials and Methods

Study Overview. The study was conducted from February of 2014 to December of 2017 at the American Family Children's Hospital, University of Wisconsin, School of Medicine and Public Health and was approved by the institutional ethics review board. Our goal was to

Figure 1. Serum hemoglobin, ferritin, and transferrin saturation at baseline and at various time points after starting IVIS infusions.

* p < 0.05

study the effect of correction of IDA on HRQL in children with IBD. The primary objective was to determine if correction of IDA improves HRQL in children with IBD. Our secondary objective was to compare this effect in children who were newly started on infliximab with the effect in those already established on infliximab treatment. Inclusion criteria were iron deficiency, age of 0 to 18 years, diagnosis of Crohn disease or ulcerative colitis, and treatment with infliximab. Exclusion criteria were folate and B12 deficiencies. We elected to conduct the study in patients receiving infliximab for practical reasons to take advantage of the intravenous access for infliximab infusions to administer IVIS.

Patients were consecutively recruited as they arrived to the pediatric infusion center for infliximab infusions. After obtaining informed consent from the parents and assent from the patients, demographic and clinical data were collected, patients and parents received HRQL surveys, an intravenous line was placed for infliximab treatment, and blood was drawn for laboratory studies as part of the standard of care. Pediatric Crohn disease

and ulcerative colitis activity indices (PCDAI and PUCAI, respectively) were also calculated at this time. These assessments were repeated prior to each infliximab infusion, but HRQL surveys were administered every 4 months. According to a protocol²² already established to efficiently correct IDA in children with IBD, iron-deficient patients continued to receive 3 mg/kg, to a maximum of 200 mg IVIS (Venofer, American Regent Inc, Shirley, NY), following infliximab infusions (administered every 3 to 8 weeks, depending on patient response), until they had two consecutive laboratory studies without evidence of iron deficiency. Changes in laboratory parameters and HRQL over time and association between these changes were analyzed in the entire cohort and compared with those of patients who were started on the IVIS protocol at or during infliximab induction and to those who had already been established on infliximab at the time of enrollment.

Laboratory Studies. Hemoglobin (Hb), transferrin saturation (TSAT), ferritin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and serum albu-

Table 2. Summary of Linear Trends in Outcome Parameters from Baseline to Month 36

	Slope Estimate*	95% CI	p value†
Laboratory parameters			
Hemoglobin	0.0567	0.0347–0.0788	<0.0001
Ferritin	1.8386	1.1314–2.5458	<0.0001
Transferrin saturation	0.6037	0.4077–0.7996	<0.0001
Albumin	0.0068	0.0003–0.0132	0.0389
ESR	−0.1926	0.3676–0.0176	0.0312
CRP‡	0.0863	0.0226–0.1500	0.0079
Disease activity scores			
PCDAI/PUCAI§	0.2438	0.1315–3.1967	<0.0001
Patient-reported HRQL score			
Psychosocial	0.3268	0.0653–0.5883	0.0147
Emotional	0.3803	0.0540–0.7067	0.0227
Social	0.2139	−0.0435–0.4713	0.1027
School functioning	0.3514	0.0038–0.6989	0.0476
Physical	0.4540	0.1813–0.7267	0.0013
Total	0.3921	0.1466–0.6376	0.0019
Parent-reported HRQL score			
Psychosocial	0.4987	0.1889–0.8086	0.0018
Emotional	0.4862	0.1197–0.8526	0.0097
Social	0.4232	0.1075–0.7388	0.0089
School functioning	0.5138	0.1074–0.9202	0.0136
Physical	0.4675	0.1499–0.7851	0.0042
Total	0.4949	0.1959–0.7939	0.0013

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HRQL, health-related quality of life; PCDAI, Pediatric Crohn Disease Activity Index; PUCAI, Pediatric Ulcerative Colitis Activity Index

* Slope parameter for outcome parameter on follow-up month using a linear mixed-effects model or a generalized mixed-effects model. Follow-up month, age, sex, and intravenous iron sucrose time (at or during induction versus after induction) were included as covariates.

† p values of <0.05 are shown in bold.

‡ Proportion of patients with normal CRP.

§ Proportion of patients with PCDAI/PUCAI consistent with remission or mild disease.

min were measured by routine methods in the hospital clinical laboratory. Anemia was defined according to general World Health Organization criteria as Hb < 11.5 g/dL in patients less than 11 years of age and <12 g/dL in females and <13 g/dL in males 11 years of age and older. Iron deficiency was defined as either low ferritin or TSAT, according to the following cut-off values: ferritin of <100 ng/mL with elevated CRP, <30 ng/mL with normal CRP, and TSAT of <20% regardless of CRP.²⁵ Upper limits of normal for ESR were 15 mm/hr for males and 20 mm/hr for females. As a result of modification of laboratory procedures, upper limits of normal for CRP changed several times during the study; therefore, changes in CRP over the course of the study were analyzed in terms of the proportion of patients in the cohort with normal values at each time point. For albumin, 3.2 and 3.3 g/dL were considered the lower limits of normal for patients

above 8 years of age and for those between 6 and 8 years of age, respectively (there were no participants less than 6 years of age in the study).

Assessment of Disease Activity and HRQL. Disease activity was assessed with CRP, ESR, albumin, and PCDAI²⁶ and PUCAI,²⁷ respectively. For both PCDAI and PUCAI, scores below 10 are consistent with remission. Scores from 10 to 30 (PCDAI) or from 10 to 34 (PUCAI) indicate mild disease. As a result of the different scales for the two indices we have analyzed changes over time in terms of the proportion of patients in remission or mild disease activity, with PCDAI scores of 0 to 30 and PUCAI scores from 0 to 34 (henceforth referred to as “low disease activity scores”) and values above these cut-offs indicating more severe disease (henceforth referred to as “high disease activity scores”) at each particular time point. Only patients with normal CRP,

Table 3. Comparison of Linear Trends in Outcome Parameters from Baseline to Month 36 between New and Established IFX Treatment Groups

	New IFX (n = 11)			Established IFX (n = 27)			p value†
	Slope Estimate*	SE	p value†	Slope Estimate*	SE	p value†	
Laboratory parameters							
Hemoglobin	0.1286	0.0295	<0.0001	0.0377	0.0116	0.0014	0.0012
Ferritin	1.3410	0.5164	0.0125	2.0161	0.4340	<0.0001	0.3306
Transferrin saturation	1.0543	0.2844	0.0005	0.4707	0.0930	<0.0001	0.0123
Albumin	0.0109	0.0068	0.117	0.0050	0.0037	0.1772	0.0030
ESR	−0.2164	0.0667	0.0021	−0.1531	0.1133	0.1785	0.2871
CRP§	NA¶			0.0913	1.0268	0.6264	NA
Disease activity scores							
PCDAI/PUCAI#	0.4795	0.2595	0.0647	0.2170	0.0474	<0.0001	0.2244
Patient-reported HRQL score							
Psychosocial	0.4085	0.2633	0.1306	0.2837	0.1475	0.0569	0.5501
Emotional	0.8242	0.3518	0.0255	0.2858	0.1879	0.1309	0.2697
Social	0.0032	0.3413	0.9926	0.2255	0.1331	0.0931	0.8293
School functioning	0.5117	0.3757	0.1827	0.2979	0.1995	0.1382	0.5890
Physical	0.8746	0.4396	0.0552	0.2843	0.1176	0.0172	0.0529
Total	0.5897	0.2989	0.0572	0.3130	0.1305	0.0181	0.2777
Parent-reported HRQL score							
Psychosocial	0.6679	0.3202	0.0451	0.3934	0.1697	0.0222	0.2889
Emotional	1.2229	0.3539	0.0016	0.3089	0.2114	0.1467	0.0666
Social	0.3153	0.3879	0.4223	0.3698	0.1576	0.0207	0.5363
School functioning	0.5229	0.3939	0.1938	0.4286	0.2264	0.0608	0.5526
Physical	1.3308	0.4044	0.0024	0.2208	0.1531	0.1520	0.0037
Total	0.7761	0.3370	0.0279	0.3533	0.1555	0.0250	0.1258

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HRQL, health-related quality of life; IFX, infliximab; PCDAI, Pediatric Crohn Disease Activity Index; PUCAI, Pediatric Ulcerative Colitis Activity Index

* Slope parameter for outcome parameter on follow-up month using a linear mixed-effects model or a generalized mixed-effects model. Follow-up month, age, and sex were included as covariates.

† p value for evaluating slope within each group; Bolded values represent p values of <0.05.

‡ p value for comparing slopes between new and established IFX treatment groups; Bolded values represent p values of <0.05.

§ Proportion of patients with normal CRP.

¶ NA indicates insufficient data for analysis.

Proportion of patients with low PCDAI/PUCAI.

ESR, and albumin were considered to be in remission.

Health-related quality of life was assessed with PedsQL 4.0 (Pediatric Quality of Life Inventory) Generic Core Scales.^{28,29} Health-related quality of life is defined as the patient's subjective perception of the impact of his/her chronic illness on physical and psychosocial well-being. It can be assessed with disease-specific or generic surveys.³⁰ Generic surveys such as PedsQL 4.0 assess areas of physical and psychosocial functioning relevant for both healthy and ill populations and allow comparisons between patients with different diseases.³⁰ In pediatric IBD patients, the validity of PedsQL 4.0 has been established.⁷ We elected to use this

generic survey to allow future comparative analysis of the effect of correction of IDA on HRQL between various diseases. PedsQL 4.0 scores (range, 0–100, higher scores indicate better HRQL) represent child-reported and parent-reported psychosocial, physical, and total scales.²⁸ The psychosocial score is derived from emotional, social, and school functioning subscores.

Analysis of Data. Laboratory results and quality of life scores were summarized in terms of means ± standard deviations. Comparisons of baseline laboratory values between infliximab treatment groups were done using a 2-sample t-test. Postbaseline data were categorized in 3-months intervals, including values obtained within

Figure 2. Proportion of patients with normal C-reactive protein and PCDAI/PUCAI consistent with remission or mild disease at various time points after starting IVIS infusions.

PCDAI, Pediatric Crohn Disease Activity Index; PUCAI, Pediatric Ulcerative Colitis Activity Index.

■ CRP; ■ PCDAI/PUCAI

* $p < 0.05$

± 1.5 months of each time point. A linear mixed-effects model with patient-specific random effects and an autoregressive correlation structure was used to evaluate changes in laboratory parameters measured on a continuous scale and quality of life scores over time. Analogously, changes in the proportions of patients with normal CRP levels and proportion of patients with PCDAI/PUCAI consistent with remission or mild disease were evaluated using a generalized linear mixed-effects model with patient-specific random effects and a logit link function. Changes in laboratory values and quality of life score over time were quantified by calculating subject-specific slope parameters. Pearson correlation analysis was conducted to evaluate the association between changes in laboratory values and changes in quality of life scores. All reported p values are 2-sided, and $p < 0.05$ was used to define statistical significance. Statistical analysis was conducted using SAS software (SAS Institute Inc, Cary, NC), version 9.4.

Results

Baseline Demographic and Clinical Data. A summary of demographic and clinical data, including sex, age, diagnosis, baseline laboratory parameters, disease activity, and HRQL scores, is presented in Table 1. Thirty-nine patients were enrolled; 1 patient withdrew from the study before the first follow-up. No patient was otherwise excluded. Results represent data from 38 patients. The age range at enrollment was 6 to 18 years. The majority of patients had Crohn disease. Most participants had already been on maintenance doses of infliximab ("established infliximab treatment group"), and 29% had not completed infliximab induction at the time of enrollment ("new infliximab treatment group"). In the new treatment group infliximab was started after initial diagnosis in 3 patients. Reasons for switching to

infliximab from other drugs included nausea and vomiting (1 patient) or poor growth (1 patient) on azathioprine; painful injection site with adalimumab (1 patient); and persistent disease on azathioprine (3 patients), methotrexate (1 patient), or mesalamine (1 patient).

The mean $\pm$ SD number of months patients spent in the study was 19 ± 13 (range, 2–46). The 38 participants received a total of 249 IVIS infusions; mean $\pm$ SD per individual patient was 6.6 ± 4.4 (range, 1–22). The mean $\pm$ SD number of IVIS infusions per patient per month was 0.5 ± 0.3 (range, 0.1–1.4). Three patients had adverse reactions, including 1 patient with headache, 1 with nausea after infusion, and 1 with chest tightness and pressure during infusion. The headache developed after the second iron sucrose infusion, and the patient had not received more iron sucrose infusions after that. He continued to have periodic, at times severe, headaches for more than 2 years. These tended to occur following subsequent infliximab infusions, so it is not clear if they were related entirely to iron sucrose. The patient who reported nausea continued to receive iron sucrose with no further nausea reported. For the patient with chest pain and tightness the infusion was paused and then started at half rate. This was tolerated well. TUMs were given for symptom relief out of concern for acid reflux symptoms. Subsequent infusions have been given with no further chest pain or tightness.

As shown in Table 1, at baseline patients in the new infliximab treatment group had significantly more severe anemia compared with those in the established infliximab treatment group ($p < 0.001$). The parent-reported emotional and physical scores were also significantly lower in this group, ($p = 0.036$ and $p = 0.048$, respectively). There was no significant difference in other HRQL scores. Similarly, there was no statistically significant difference in other baseline parameters

Figure 3. Patient and parent reported changes in HRQL scores from baseline at various time points after starting IVIS infusions.

HRQL, Health-related quality of life

□ psychosocial scores; ■ physical scores; ■ total scores.

* p < 0.05

between the 2 groups, including albumin, TSAT, ferritin, PCDAI scores, ESR, and proportion of patients with normal CRP.

Changes in Hematology Indices. Figure 1 shows an overview of mean Hb and iron indices at baseline and at various time points after starting IVIS infusions. Mean Hb levels rose to 12.68 and 12.86 mg/dL by 3 and 6 months, respectively, then normalized and remained normal (above 13 mg/dL) throughout the study. Both mean ferritin and TSAT normalized by 3 months and remained normal (above 30 ng/mL and 20%, respectively) throughout the study. All 3 parameters were significantly higher compared with baseline values at all time points except for TSAT at 33 months.

Table 2 shows the summary of linear trends for the entire cohort in Hb and iron indices from baseline to 36 months, as calculated by the correlation coefficients

of each versus time. All 3 parameters increased significantly. As shown in Table 3, this was also true for both infliximab treatment groups, but there were significantly higher increases in Hb and TSAT in the new compared with the established infliximab treatment group. At the same time there was no significant difference in the rise of ferritin between the 2 groups.

Changes in Disease Activity Markers. The proportion of patients with normal CRP and PCDAI/PUCAI consistent with remission or mild disease was between 80% and 90% during the first 12 months, and then both increased to 100% from 18 months on (Figure 2). Accordingly, as shown in Table 2, linear trend analysis showed significant improvement from baseline to 36 months in CRP, PCDAI/PUCAI, and ESR for the entire cohort.

Table 3 shows separate analysis of the new and established infliximab treatment groups. There was

Figure 4. Patient and parent reported changes in psychosocial subscores from baseline at various time points after starting IVIS infusions.

□ emotional; ■ social; ■ school functioning.

* p < 0.05

significant improvement in ESR and a significantly larger increase in serum albumin in the new infliximab treatment group compared with the established infliximab treatment group. However, the improvement in PCDAI/PUCAI was not statistically significant in the new infliximab treatment group. In contrast, in the established infliximab treatment group there was no significant change over time in ESR and CRP, but significant improvement occurred in PCDAI/PUCAI.

Changes in HRQL. There was a significant increase in both patient-reported and parent-reported mean physical and total HRQL scores and the parent-reported school functioning subscore by 3 months (Figures 3 and 4). Improvements were maintained with few exceptions at various time points during the remainder of the study, with most of the significant changes occurring in parent-reported scores (Figure 3 and 4).

Linear trends from baseline to 36 months showed significant improvement in all except the patient-

reported social scales in the entire cohort (Table 2). Table 3 shows linear trends according to infliximab treatment group. In both groups there was significant improvement in parent-reported psychosocial and total scores. The patient-reported physical and total score improved significantly in the established but not in the new infliximab treatment group. Both patient-reported and parent-reported emotional scores improved significantly in the new but not in the established infliximab treatment group, while the parent-reported social score showed significant improvement only in the latter group. Overall there was no statistically significant difference between the 2 groups in the degree of improvement, except that there was significantly larger improvement in parent-reported physical scores in the new infliximab treatment group.

Correlation Between Changes in Hemoglobin and HRQL. Significant positive correlations were found between the increases in Hb and improvements in

Figure 5. Changes in hemoglobin versus changes in parent-reported PedsQL scores over time.

(A) psychosocial; (B) emotional; (C) social; (D) school; (E) physical; and (F) total.
Hb, hemoglobin; HRQL, health-related quality of life.
■ Hb; ■ HRQL.

parent-reported emotional ($r = 0.36$, $p = 0.0256$) and physical scores ($r = 0.33$, $p = 0.045$) (Figure 5B and E). The remainder of parent-reported (Figure 5A, C, D, and F) and all patient-reported (not shown) HRQL scores showed a similar improving trend with correction of

IDA, but the changes were not statistically significant.

Discussion

To our knowledge this is the first long-term study

that prospectively evaluates the correlation between correction of anemia and changes in HRQL in children with IBD receiving routine IVIS. Results confirm our previous finding²² that periodic IVIS can be used safely and effectively to gradually replenish and maintain iron stores and correct IDA in children with IBD. In our patients, most of whom had inactive or mild disease, an average of 1 IVIS infusion per 2 months maintained normal Hb, ferritin, and TSAT in the long term. This interval is similar to the usual frequency of infliximab treatments, making this approach practical and convenient for patients treated with infliximab.

There was a trend of substantial improvement in most HRQL scores over the course of the study, along with correction of IDA. Moreover, ESR, CRP, and disease activity scores also improved, with the greatest improvement of ESR noted in the new infliximab treatment group. This suggests that, especially in this group, better disease control was an important contributor to improvements in HRQL, particularly in physical HRQL scores. This finding is in agreement with those of a recent study demonstrating a significant positive correlation between improvement of inflammatory biomarkers and improved HRQL in children with IBD treated with biologicals.^{8,31,32} Improvement of HRQL associated with infliximab treatment was also shown in a large adult retrospective study.³³ Nonetheless, starting infliximab treatment per se did not appear to be the sole contributor to improvements in HRQL in the entire cohort since most patients had already been on infliximab for variable lengths of time and had been stable clinically at the time of enrollment.

The individual role of anemia in HRQL of pediatric IBD patients is not well understood, in part because of the close association between the severity of anemia and disease activity. In this study, the significant improvements in HRQL scores in the established infliximab treatment group without simultaneous changes in ESR, CRP, and serum albumin suggest that correction of anemia was an important independent contributor to improvements in HRQL. This is in agreement with adult data^{9,17–20} demonstrating a similar benefit. Interestingly, improvement in IBD symptoms has been observed¹⁷ in adults treated with intravenous iron and was hypothesized to be related to the effect of iron supplementation on general well-being. Since hematocrit and general well-being are significant components of the PCDAI score, improved PCDAI in the established infliximab treatment group was likely at least in part related to correction of IDA. Regardless, a limitation of our study is the lack of a contemporaneous or historical infliximab-only control group, or a control group on other maintenance treatment, to further confirm that the addition of IVIS led to improvements in HRQL not seen with infliximab alone. A further limitation is the lack of endoscopic and fecal calprotectin data for more accurate assessment of

disease activity. We may have underestimated disease activity, especially in the second half of the study, when the conventional inflammatory markers were consistent with remission. However, such underestimation would only strengthen the potential contribution of correction of anemia to improvements in HRQL. Finally, our cohort was relatively small, and especially beyond the 2-year time point the number of data points available for analysis was relatively low.

Our findings have potentially important implications for quality of care goals in the management of pediatric IBD. They suggest that anemia may be one of the important and correctable contributors to impaired HRQL in these children. Larger studies are needed to further explore this relationship, especially in quiescent IBD, given the high prevalence of anemia in children with IBD even years after diagnosis.⁴ Anemia-free remission should be considered as a quality of care indicator in pediatric IBD patients.

ARTICLE INFORMATION

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