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Fecal Calprotectin Assay at an Early Stage of Treatment Can Be Used as a Surrogate Marker to Predict Clinical Remission and Mucosal Healing in Pediatric Crohn's Disease

Yeoun Joo Lee and Jae Hong Park

Department of Pediatrics, Pusan National University School of Medicine, Yangsan, Korea

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Correspondence to
Jae Hong Park
Department of Pediatrics, Pusan National University Yangsan Hospital, 20 Geumo-ro, Mulgeum-eup, Yangsan 50612, Korea.
Email: jhongpark@pusan.ac.kr

ORCID iDs
Yeoun Joo Lee
https://orcid.org/0000-0001-8012-5433
Jae Hong Park
https://orcid.org/0000-0002-5274-7064

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Purpose: This study evaluated the predictive role of fecal calprotectin (FC) measured at an early stage of treatment for monitoring clinical remission (CR) after six months and endoscopic remission (ER) after one year of treatment in pediatric Crohn's disease (CD).
Methods: This retrospective study included 45 patients who simultaneously underwent ileocolonoscopy and FC testing during follow-up. FC levels were measured before and after six weeks of treatment. CR was assessed after six months of treatment using Pediatric Crohn's Disease Activity Index and acute-phase reactants. ER was assessed after one year using the Simple Endoscopic Score for Crohn's Disease.
Results: Twenty-nine (64.4%) patients used oral prednisolone for remission induction and 16 (35.6%) patients used anti-tumor necrosis factor-alpha. Thirty (66.7%) patients achieved CR, while 24 (53.3%) achieved ER. The FC level measured after six weeks of treatment could predict CR (χ^2=9.15, p=0.0025) and ER (χ^2=12.31, p=0.0004). The δFC could predict CR (χ^2=7.91, p=0.0049), but not ER (χ^2=1.85, p=0.1738). With a threshold of ≤950.4 μg/g, FC at week six could predict CR with 76.7% sensitivity and 73.3% specificity. The area under the curve (AUC) was 0.769 (standard error 0.0773, p=0.0005). The same threshold predicted ER with 87.5% sensitivity and 71.4% specificity. The AUC was 0.774 (standard error 0.074, p=0.0002).
Conclusion: FC assay at an early stage of treatment can be used as a surrogate marker to predict CR and mucosal healing in pediatric CD.

Keywords: Leukocyte L1 Antigen Complex; Crohn disease; Child; Biomarker

INTRODUCTION

Crohn's disease (CD) is caused by chronic mucosal inflammation of the intestine and characterized by variable disease activity, often with intermittent periods of disease relapse and remission. Early identification of treatment response can facilitate the timely management of patients with CD. Mucosal healing is considered the best predictor of

favorable long-term outcomes in children with CD [1]. The assessment of symptoms has not proven useful in accurately establishing endoscopic activity despite the availability of instruments such as the Pediatric Crohn's Disease Activity Index (PCDAI). C-reactive protein (CRP) is also not an accurate marker of mucosal healing [2]. Additionally, repeated endoscopic or radiological assessments are not always feasible. As the treatment goal in CD has shifted to "treat-to-target" paradigms that strictly control inflammation, the need for a sensitive, accurate, and reliable method for measuring disease activity has emerged.

Fecal calprotectin (FC) is a highly sensitive disease activity biomarker in inflammatory bowel disease (IBD). It can quantify inflammation of the intestinal mucosa at an early stage before serological markers can be detected [3]. FC values have shown a strong correlation with CD activity, as measured by clinical, endoscopic, and histological indices [4-6]. It is also useful for identifying patients in deep remission with lower probabilities of relapsing in the short term [7] and patients at high risk of disease recurrence postoperatively [8].

A retrospective cohort study demonstrated that early changes in FC could predict primary non-response to anti-tumor necrosis factor-alpha (anti-TNF-α) therapy in adult patients with CD [9]. These results suggest that a drop in FC <70% after induction predicts primary non-response to anti-TNF-α. A prospective study reported that the FC assay after anti-TNF-α induction could be used as a marker to predict sustained clinical response and mucosal healing after one year [10]. In a study of Korean adults with CD receiving anti-TNF-α, when FC was measured together with serum CRP and albumin levels, the accuracy was high in predicting deep healing [11]. A prospective longitudinal cohort study demonstrated that consecutive measurements of FC could predict flares in IBD patients undergoing maintenance therapy with anti-TNF-α [12]. In a cohort of 53 pediatric CD patients receiving anti-TNF-α maintenance therapy, consecutive FC measurements helped predict clinical relapse [13]. However, data on its accuracy in predicting clinical remission (CR) and endoscopic remission (ER) in pediatric CD are scarce. Therefore, this study aimed to evaluate the predictive role of FC values measured six weeks after treatment with steroids or anti-TNF-α in a pediatric CD for monitoring CR after six months and ER after one year.

MATERIALS AND METHODS

Study design

A single-center retrospective study was conducted by reviewing the medical records of 45 patients aged ≤18 years, diagnosed with CD, who had FC measurements between January 2013 and June 2018, and had regular follow-up for more than one year at Pusan National University Children's Hospital. CD is diagnosed based on a combination of clinical, endoscopic, radiological, and histopathological criteria.

All the patients initially received conventional therapy. Because of the government insurance policy, the medications were changed according to the step-up strategy if no CR or relapse of the disease occurs during treatment. Therefore, all 16 patients who achieved remission induction with anti-TNF-α in this study were those who did not respond to conventional treatment.

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FC measurement

FC measurements (ImmunoCAP 250; Phadia, Uppsala, Sweden, fluorescent enzyme immunoassay, values μg/g feces) were performed on stool samples before treatment with prednisolone or anti-TNF-α and six weeks later. Patients were instructed to collect stool samples from the first bowel movement of the day and deliver them to the hospital within 24 hours. Delta FC (δFC) was calculated as follows: (FC pre-treatment – FC 6 weeks post-treatment)×100/(FC pre-treatment), as a percentage.

Data collection and definitions

Clinical activity, measured using the PCDAI, was assessed before treatment. Reference standards for disease activity and location were determined using endoscopy, capsule endoscopy, magnetic resonance imaging, computed tomography, or a combination of these. Disease location and behavior at diagnosis were defined according to the Paris Classification as follows: disease location according to the Paris classification. L1=distal 1/3 ileum±limited cecal disease, L2=colonic disease, L3=ileocolonic disease, L4a=upper disease proximal to the ligament of Treitz, L4b=upper disease distal to the ligament of Treitz; and proximal to the distal 1/3 ileum. L4a and L4b are designated, in addition to distal ileal and/or colonic diseases. Clinical behavior according to the Paris classification. B1=nonstricturing, nonpenetrating, B2=structuring, B3=penetrating, B2B3=both penetrating and stricturing disease, either concurrently or separately. P=perianal disease modifier; perianal disease was defined as the presence of a fistula or abscess.

CR was assessed after six months of treatment and ER after one year. CR was defined as a PCDAI <10 and a normal erythrocyte sedimentation rate (ESR) or CRP level. Ileocolonoscopy was performed before treatment and after one year to assess mucosal healing. ER was defined as Simple Endoscopic Score for Crohn's Disease (SES-CD) ≤2 [14].

FC values obtained six weeks after treatment were compared in relation to the presence or absence of CR after six months of treatment. FC values measured six weeks after treatment were also compared with respect to the presence or absence of ER after one year of treatment. The FC values measured six weeks after treatment with regard to the type of drug used to induce remission were compared. The correlation between baseline FC values and CR after six months and ER after one year of treatment was investigated. The CR rate after six months of treatment and the ER rate after one year were compared according to the type of drug used to induce remission. The relationship between δFC after six weeks of treatment with CR and ER and the relationship between drugs for remission induction and δFC were investigated.

Statistical analysis

A univariate Cox regression analysis was performed to evaluate whether FC could serve as an independent predictor of CR and ER. Receiver operating characteristic (ROC) curve analysis was used to determine the specificity, sensitivity, and optimal threshold values of FC. The accuracy of FC was evaluated using the area under the curve (AUC) of the ROC. The median values of initial FC, FC at the sixth week, and δFC (%) were used for the logistic regression analysis. The Mann–Whitney U-test was used to compare the categorical variables. All numerical data are expressed as mean±standard deviation. Statistical analyses were performed using commercially available software (version 19.0.7; MedCalc Software, Ostend, Belgium). Statistical significance was set at $p<0.05$.

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Ethical consideration

This study was approved by the Institutional Review Board of the Pusan National University Yangsan Hospital (No. 05-2020-012). The investigator collected and recorded the data in such a manner that the subjects could not be identified directly or through identifiers linked to them.

RESULTS

Patient characteristics

The male:female ratio was 32:13. The mean age of patients was 13.48±2.75 (5.38–17.65) years (median age=13.48 years). Both abdominal pain and diarrhea were the most common presenting symptoms, occurring in 37 patients (82.2%). Elevation of acute-phase reactants was observed in 86.7% (ESR) and 83.7% (CRP) patients. Anemia and hypoalbuminemia were observed in 22 (48.9%) and 18 (40.0%) patients, respectively. The disease location of CD at diagnosis was L1 in two (4.4%) patients, L2 in two (4.4%), and L3 in 41 (91.1%). Both L4A and L4B were diagnosed in 55.6% patients. The clinical behavior at diagnosis was B1 in 30 (66.7%) patients, B2 in 14 (31.1%), B3 in one (2.2%), B2B3 in one (2.2%), and P in 32 (71.1%). Thirty-six patients (80.0%) had "moderate-to-severe CD" (PCDAI ≥30). Twenty-nine (64.4%) patients had severe "endoscopic disease severity" (SES-CD >15), and 13 (28.9%) had moderate severity (SES-CD 7-15). The clinical characteristics of the patients are summarized in **Table 1**.

Treatment details and FC levels in each patient group

Twenty-nine (64.4%) and 16 (35.6%) patients received oral prednisolone and anti-TNF-α for remission induction, respectively. For maintenance therapy, eight (27.6%) patients treated with oral prednisolone for remission induction received 5-ASA, 11 (37.9%) received immunomodulators, and 10 (34.5%) received anti-TNF-α. In contrast, drug optimization (interval shortening) was found in three (18.8%) patients treated with anti-TNF-α for remission induction. After six months of treatment, 30 (66.7%) patients achieved CR (induction with oral prednisolone, 62.1%; induction with anti-TNF-α, 87.5%). ER was achieved in 24 (53.3%) patients after one year (induction with oral prednisolone, 41.4%; induction with anti-TNF-α, 62.5%). All patients had elevated FC levels prior to the start of treatment. The median baseline FC level was 1,927.2 (68.1–27,903.0) μg/g, and the median FC level after six weeks of treatment was 666.0 (0–2,000) μg/g (**Table 2**).

The baseline FC level did not show an association with CR (χ^2=1.17, p=0.2906) or ER (χ^2=0.19, p=0.661). No statistically significant difference was observed in remission rates after treatment between the oral prednisolone and anti-TNF-α groups (CR after six months, p=0.1280 and ER after one year, p=0.5004). No statistical difference was found in δFC measured six weeks after treatment between the two groups using anti-TNF-α and oral prednisolone for remission induction (80.0 vs. 52.5%) (p=0.3550) (**Table 3**).

Median FC after six weeks in patients with CR was significantly lower than in those without CR (486.5 vs. 1,504.0 μg/g) (p=0.0025). The median FC level after six weeks was significantly lower in patients with ER than in those without ER (373.0 vs. 1,500.0 μg/g) (p=0.0004). No significant difference was found between the groups using anti-TNF- and oral prednisolone for remission induction (473.5 vs. 950.4 μg/g) in FC measured after six weeks (p=0.7479). The δFC measured six weeks after treatment in patients with CR was significantly higher than that in those without CR (81.1 vs. 6.4%) (p=0.0049). However, there was no statistical difference

Table 1. Baseline characteristics of patients with Crohn's disease

Characteristic	Value (n=45)
Age (yr)	13.48±2.75 (5.38–17.65)
Male:female	32:13
Presenting symptoms	
Abdominal pain	37 (82.2)
Diarrhea	37 (82.2)
Weight loss	31 (68.9)
Hematochezia	17 (37.8)
Fever	11 (24.4)
Laboratory findings	
ESR elevation	39/45 (86.7)
High CRP	36/43 (83.7)
Anemia	22/45 (48.9)
Hypoalbuminemia	18/45 (40.0)
ASCA positive	14/37 (37.8)
Disease location*	
L1	2 (4.4)
L2	2 (4.4)
L3	41 (91.1)
L4a	25 (55.6)
L4b	25 (55.6)
Disease behavior†	
B1	30 (66.7)
B2	14 (31.1)
B3	1 (2.2)
B2B3	1 (2.2)
Obstruction	3 (6.7)
Perianal	32 (71.1)
Clinical disease severity PCDAI	
Mild <30	9 (20.0)
Moderate to severe ≥30	36 (80.0)
Endoscopic disease severity	
Mild (SES-CD 3–6)	3 (6.7)
Moderate (SES-CD 7–15)	13 (28.9)
Severe (SES-CD >15)	29 (64.4)

Values are presented as mean±standard deviation (range), number only, or number (%).
ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, ASCA: anti-Saccharomyces cerevisiae antibody, PCDAI: Pediatric Crohn's Disease Activity Index, SES-CD: Simple Endoscopic Score for Crohn's Disease.
*Disease location according to the Paris classification. L1=distal 1/3 ileum±limited cecal disease, L2=colonic disease, L3=ileocolonic disease, L4a=upper disease proximal to the ligament of Treitz, L4b=upper disease distal to the ligament of Treitz; and proximal to the distal 1/3 ileum. According to the Paris classification, L4a and L4b are designated in addition to distal ileal and/or colonic diseases. †Clinical behavior according to the Paris classification. B1=nonstricturing, nonpenetrating, B2=structuring, B3=penetrating, B2B3=both penetrating and stricturing disease, either at the same time or at different times. Perianal=perianal disease modifier; perianal disease was defined as the presence of a fistula or abscess.

in δFC measured six weeks after treatment between patients with and without ER after one year (84.8 vs. 24.8%) (p=0.1738) (**Table 4**).

Accuracy of FC for the prediction of CR and ER

The FC level measured after six weeks of treatment could predict CR (χ^2=9.15, p=0.0025) and ER (χ^2=12.31, p=0.0004). The δFC could predict CR (χ^2=7.91, p=0.0049), but not ER (χ^2=1.85, p=0.1738). With a threshold of ≤950.4 μg/g, FC at the sixth week could predict CR with 76.7% sensitivity and 73.3% specificity. The AUC was 0.769 (standard error 0.0773, p=0.0005) (**Fig. 1**). The ER could also be predicted using the same threshold with 87.5% sensitivity and 71.4% specificity. The AUC was 0.774 (standard error of 0.074, p=0.0002) (**Fig. 2**).

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Table 2. Treatment details and median fecal calprotectin level

Treatment drug and outcome	Value
Main drug for RI	
Oral prednisolone	29/45 (64.4)
Anti-TNF-α	16/45 (35.6)
Main drug for maintenance therapy in patients treated with oral prednisolone for RI	
5-ASA	8/29 (27.6)
Immunomodulator	11/29 (37.9)
Anti-TNF-α	10/29 (34.5)
Optimization of anti-TNF-α during 1 year of treatment in patients with anti-TNF-α for RI	
Interval shortening	3/16 (18.8)
Rate of CR after 6 months of treatment according to mediations for RI	30/45 (66.7)
Rate of ER after 1 year of treatment according to medications for RI	24/45 (53.3)
Median FC level (μg/g)	
Baseline	1,927.2 (68.1–27,903.0)
After 6 weeks of treatment	666.0 (0–2,000)

Values are presented as number (%) or median (range).
RI: remission induction, Anti-TNF-α: anti-tumor necrosis factor alpha, CR: clinical remission, ER: endoscopic remission, FC: fecal calprotectin.

Table 3. Comparison of treatment response and the δFC level according to the drug for remission induction

Variable	Oral PRS (n=29)	Anti-TNF-α (n=16)	*p*-value
Rate of CR after 6 months of treatment	18 (62.1)	14 (87.5)	0.1280
Rate of ER after 1 year of treatment	12 (41.4)	10 (62.5)	0.5004
δFC measured at 6 weeks after treatment (%)	52.5	80.0	0.3550

Values are presented as number (%).
Delta FC (δFC) was calculated as follows: (FC pre-treatment – FC 6 weeks post-treatment)×100/(FC pre-treatment), as a percentage.
PRS: prednisolone, Anti-TNF-α: anti-tumor necrosis factor alpha, CR: clinical remission, ER: endoscopic remission, FC: fecal calprotectin.

Table 4. Median value of FC and the δFC measured at 6 weeks after treatment according to drug and treatment response in patients with Crohn's disease

Variable	Type of drug for RI			CR at 6 months after RI			ER at 1 year after RI		
	Anti-TNF-α	Oral PRS	*p*-value	(+)	(–)	*p*-value	(+)	(–)	*p*-value
FC (μg/g)	473.5	950.4	0.7479	486.5	1,504.0	0.0025	373.0	1,500.0	0.0004
δFC (%)	80.0	52.5	0.3550	81.1	6.4	0.0049	84.8	24.8	0.1738

δFC was calculated as follows: (FC pre-treatment – FC 6 weeks post-treatment)×100/(FC pre-treatment), as a percentage.
FC: fecal calprotectin, δFC: delta FC, RI: remission induction, CR: clinical remission, ER: endoscopic remission, Anti-TNF-α: anti-tumor necrosis factor alpha, PRS: prednisolone.

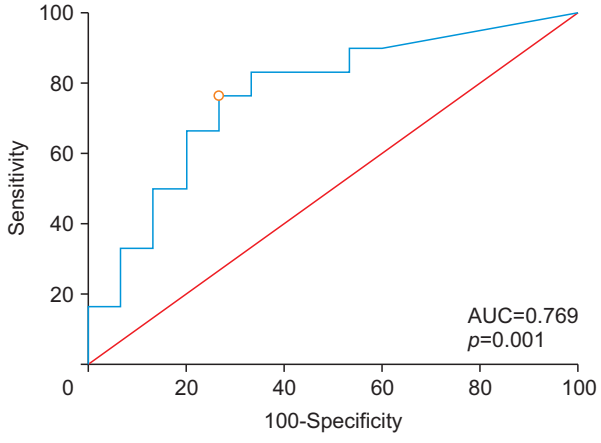

Fig. 1. Receiver operating characteristic analysis of fecal calprotectin was performed at six weeks to predict clinical remission at six months after treatment. A cut-off value ≤950.4 μg/g of fecal calprotectin, sensitivity 76.7%, specificity 73.3%, AUC (95% confidence interval)=0.769 (0.619–0.881), *p*=0.001.
AUC: area under the curve.

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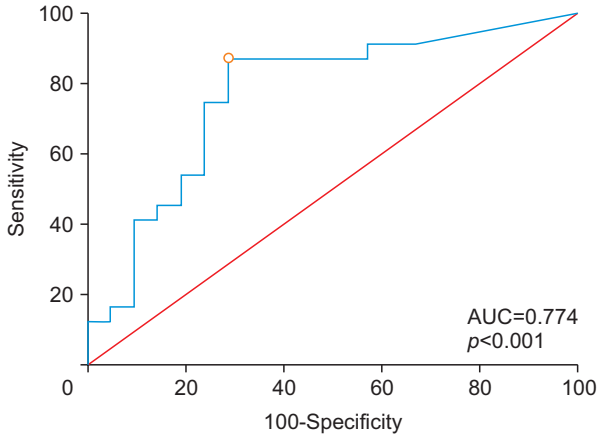

Fig. 2. Receiver operating characteristic analysis of fecal calprotectin was performed at six weeks to predict endoscopic remission at one year after treatment. A cut-off value ≤950.4 μg/g, sensitivity 87.5%, specificity 71.4%, AUC (95% confidence interval)=0.774 (0.625–0.885), p<0.001.
AUC: area under the curve.

DISCUSSION

This study aimed to evaluate whether FC measured at an early stage of treatment can predict CR and ER in children with CD who received oral prednisolone or anti-TNF-α for remission induction. The results of this study demonstrated that early changes in FC measured six weeks after the initiation of treatment are accurate predictors of CR after six months and ER after one year of treatment in pediatric CD. δFC predicted CR but not ER. The baseline FC concentration did not seem to predict CR or ER reliably. In a prospective cohort study of 24 children with luminal CD, FC measured at diagnosis and after eight weeks of therapy with exclusive enteral nutrition (EEN) or steroids demonstrated that FC <500 μg/g and FC drop >50% had higher predictive value for inactive disease [2]. However, there are conflicting reports on the prediction of the clinical response to changes in FC early after treatment. An early decrease in FC levels in children with luminal CD did not predict clinical response after six weeks of EEN induction therapy, and CR was predicted with low accuracy [15].

Kostas et al. [16] reported conflicting results where baseline FC concentrations were significantly higher in adult patients with IBD who had clinical relapse compared with those who remained in remission during follow-up. In a study of 35 adult patients with CD, the median anti-TNF-α level at week 14 and baseline FC level were independently associated with primary non-response [17]. D'Arcangelo et al. [18] reported that weighted pediatric CD activity index (wPCDAI), FC, and CRP are poor predictors of clinical and endoscopic response to anti-TNF-α therapy in children with CD. However, post-induction FC plus wPCDAI at week 14 can predict one-year clinical and endoscopic outcomes.

Thus, a reliable and objective surrogate marker of intestinal inflammation is an attractive prospect. FC is a cheap and non-invasive biomarker that correlates well with intestinal inflammation and endoscopic findings in luminal CD. In a study of 131 Korean pediatric CD patients treated with anti-TNF-α, the FC level was significantly lower in patients with mucosal healing than in those without (median 49.0 mg/kg vs. 599.0 mg/kg; p<0.001) [19]. Sipponen et al. [6,20] found that the FC value could discriminate mild, moderate, or highly active diseases according to the SES-CD classification.

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D'Haens et al. [21] reported that the FC levels below 250 μg/g had 94% sensitivity and 62% specificity in predicting mucosal healing in patients with CD. Kostas et al. [16] demonstrated a lower optimal threshold value (174 μg/g) that offered comparable sensitivity and improved specificity for assessing the presence of endoscopic inflammation. Previous studies have also reported that IBD patients in CR exhibit low FC levels, whereas patients with high FC levels are at an increased risk of relapse [22,23].

In a study of 63 adult patients with IBD, the FC level after induction with anti-TNF-α had 83% sensitivity and 74% specificity (cut-off ≤168 μg/g) for predicting a sustained clinical response at one year (p=0.0001) and 79% sensitivity and 57% specificity (cut-off ≤121 μg/g) for predicting mucosal healing (p=0.0001) [10]. A recent study evaluating the accuracy of FC in predicting IBD endoscopic activity reported that the area under the ROC curve for FC was 0.8 in CD. The best cut-off points for detecting CD activity were 54 for the low-range kit and 122 for the high-range kit (both with a sensitivity of 71% and a specificity of 75%) [24]. In this study, the prediction of CR and ER with FC presented an AUC of 0.769 and 0.774, respectively. A cut-off value of FC ≤950.4 μg/g gave 76.7% sensitivity and 73.3% specificity in CR. In the ER, the same cutoff value yielded 87.5% sensitivity and 71.4% specificity.

From our study, we determined that 950.4 μg/g was the best cutoff value for predicting CR and ER, which is rather high. This result can be inferred by considering whether the effect of the drug used for remission induction is sufficient to control intestinal inflammation. The time of FC measurement was two weeks after steroid tapering and just before the third injection of biologics, which may suggest that remission induction with steroids or two doses of biologics is not enough to induce mucosal healing in pediatric CD. Nevertheless, this result indicates that the FC value measured six weeks after treatment can help predict CR after six months and ER after one year.

The limitations of this study include its small sample size and retrospective design. Another limitation is the variation in medications taken by the patients included in this study because of the step-up strategy. Not all patients received maintenance treatment with a conventional dose of anti-TNF-α, 5-ASA, or an immunomodulator. However, there was no statistical difference in the CR (62.1 vs. 87.5%, p=0.1280) and ER (41.4 vs. 62.5%, p=0.5004) rates between the oral prednisolone and anti-TNF-α groups. There was also no difference in the FC level (950.4 vs. 473.5 μg/g, p=0.7479) and δFC (52.5 vs. 80.0%, p=0.3550) measured six weeks after treatment between the two groups. These results are likely due to relatively small number of patients but also associated with the reliability of CR based on PCDAI and serological tests. Despite a step-up strategy, 6 (20.0%) of 30 patients with CR had no ER after six months. Another reason is that no patients treated with anti-TNF-α responded to conventional treatment; therefore, some patients with intractable CD may have been included in this study. Moreover, δFC could not predict ER after one year, which is also presumed to be related to the limitations of this study. Our results require further validation by including larger and more homogeneous study populations.

In conclusion, our data demonstrate that the early FC assay six weeks after treatment with oral prednisolone or anti-TNF-α can be used as a surrogate marker to predict clinical response after six months and mucosal healing at one year in pediatric CD. This may be an indicator for clinicians to conduct early investigations to optimize patient care.

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REFERENCES

1. Peyrin-Biroulet L, Sandborn W, Sands BE, Reinisch W, Bemelman W, Bryant RV, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): determining therapeutic goals for treat-to-target. Am J Gastroenterol 2015;110:1324-38.
PUBMED | CROSSREF
2. Zubin G, Peter L. Predicting endoscopic Crohn's disease activity before and after induction therapy in children: a comprehensive assessment of PCDAI, CRP, and fecal calprotectin. Inflamm Bowel Dis 2015;21:1386-91.
PUBMED | CROSSREF
3. Tibble JA, Sigthorsson G, Foster R, Forgacs I, Bjarnason I. Use of surrogate markers of inflammation and Rome criteria to distinguish organic from nonorganic intestinal disease. Gastroenterology 2002;123:450-60.
PUBMED | CROSSREF
4. Leach ST, Day AS, Messenger R, Walters TD, Navas-López VM, Sladek M, et al. Fecal markers of inflammation and disease activity in pediatric Crohn disease: results from the ImageKids study. J Pediatr Gastroenterol Nutr 2020;70:580-5.
PUBMED | CROSSREF
5. Schoepfer AM, Beglinger C, Straumann A, Trummler M, Vavricka SR, Bruegger LE, et al. Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. Am J Gastroenterol 2010;105:162-9.
PUBMED | CROSSREF
6. Sipponen T, Kärkkäinen P, Savilahti E, Kolho KL, Nuutinen H, Turunen U, et al. Correlation of faecal calprotectin and lactoferrin with an endoscopic score for Crohn's disease and histological findings. Aliment Pharmacol Ther 2008;28:1221-9.
PUBMED | CROSSREF
7. Mooiweer E, Severs M, Schipper ME, Fidder HH, Siersema PD, Laheij RJ, et al. Low fecal calprotectin predicts sustained clinical remission in inflammatory bowel disease patients: a plea for deep remission. J Crohn's Colitis 2015;9:50-5.
PUBMED | CROSSREF
8. Wright EK, Kamm MA, De Cruz P, Hamilton AL, Ritchie KJ, Krejany EO, et al. Measurement of fecal calprotectin improves monitoring and detection of recurrence of Crohn's disease after surgery. Gastroenterology 2015;148:938-47.e1.
PUBMED | CROSSREF
9. Pavlidis P, Gulati S, Dubois P, Chung-Faye G, Sherwood R, Bjarnason I, et al. Early change in faecal calprotectin predicts primary non-response to anti-TNFα therapy in Crohn's disease. Scand J Gastroenterol 2016;51:1447-52.
PUBMED | CROSSREF
10. Guidi L, Marzo M, Andrisani G, Felice C, Pugliese D, Mocci G, et al. Faecal calprotectin assay after induction with anti-Tumour Necrosis Factor α agents in inflammatory bowel disease: prediction of clinical response and mucosal healing at one year. Dig Liver Dis 2014;46:974-9.
PUBMED | CROSSREF
11. Noh SM, Oh EH, Park SH, Lee JB, Kim JY, Park JC, et al. Association of faecal calprotectin level and combined endoscopic and radiological healing in patients with Crohn's disease receiving anti-tumour necrosis factor therapy. J Crohn's Colitis 2020;14:1231-40.
PUBMED | CROSSREF
12. Ferreiro-Iglesias R, Barreiro-de Acosta M, Lorenzo-Gonzalez A, Dominguez-Muñoz JE. Accuracy of consecutive fecal calprotectin measurements to predict relapse in inflammatory bowel disease patients under maintenance with anti-TNF therapy: a prospective longitudinal cohort study. J Clin Gastroenterol 2018;52:229-34.
PUBMED | CROSSREF

13. Foster AJ, Smyth M, Lakhani A, Jung B, Brant RF, Jacobson K. Consecutive fecal calprotectin measurements for predicting relapse in pediatric Crohn's disease patients. World J Gastroenterol 2019;25:1266-77.
PUBMED | CROSSREF

14. Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004;60:505-12.
PUBMED | CROSSREF

15. Copova I, Hradsky O, Zarubova K, Gonsorcikova L, Potuznikova K, Lerchova T, et al. Fecal calprotectin is not a clinically useful marker for the prediction of the early nonresponse to exclusive enteral nutrition in pediatric patients with Crohn disease. Eur J Pediatr 2018;177:1685-93. Erratum in: Eur J Pediatr 2018;177:1695.
PUBMED | CROSSREF

16. Kostas A, Siakavellas SI, Kosmidis C, Takou A, Nikou J, Maropoulos G, et al. Fecal calprotectin measurement is a marker of short-term clinical outcome and presence of mucosal healing in patients with inflammatory bowel disease. World J Gastroenterol 2017;23:7387-96.
PUBMED | CROSSREF

17. Beltrán B, Iborra M, Sáez-González E, Marqués-Miñana MR, Moret I, Cerrillo E, et al. Fecal calprotectin pretreatment and induction infliximab levels for prediction of primary nonresponse to infliximab therapy in Crohn's disease. Dig Dis 2019;37:108-15.
PUBMED | CROSSREF

18. D'Arcangelo G, Oliva S, Dilillo A, Viola F, Civitelli F, Isoldi S, et al. Predictors of long-term clinical and endoscopic remission in children with Crohn disease treated with infliximab. J Pediatr Gastroenterol Nutr 2019;68:841-6.
PUBMED | CROSSREF

19. Lee YM, Choi S, Choe BH, Jang HJ, Kim S, Koh H, et al. Association between fecal calprotectin and mucosal healing in pediatric patients with Crohn's disease who have achieved sustained clinical remission with anti-tumor necrosis factor agents. Gut Liver 2022;16:62-70.
PUBMED | CROSSREF

20. Sipponen T, Björkesten CG, Färkkilä M, Nuutinen H, Savilahti E, Kolho KL. Faecal calprotectin and lactoferrin are reliable surrogate markers of endoscopic response during Crohn's disease treatment. Scand J Gastroenterol 2010;45:325-31.
PUBMED | CROSSREF

21. D'Haens G, Ferrante M, Vermeire S, Baert F, Noman M, Moortgat L, et al. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. Inflamm Bowel Dis 2012;18:2218-24.
PUBMED | CROSSREF

22. Gisbert JP, Bermejo F, Pérez-Calle JL, Taxonera C, Vera I, McNicholl AG, et al. Fecal calprotectin and lactoferrin for the prediction of inflammatory bowel disease relapse. Inflamm Bowel Dis 2009;15:1190-8.
PUBMED | CROSSREF

23. Kallel L, Ayadi I, Matri S, Fekih M, Mahmoud NB, Feki M, et al. Fecal calprotectin is a predictive marker of relapse in Crohn's disease involving the colon: a prospective study. Eur J Gastroenterol Hepatol 2010;22:340-5.
PUBMED | CROSSREF

24. Jusué V, Chaparro M, Gisbert JP. Accuracy of fecal calprotectin for the prediction of endoscopic activity in patients with inflammatory bowel disease. Dig Liver Dis 2018;50:353-9.
PUBMED | CROSSREF