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Changes in Fecal Calprotectin Reflect Clinical Response in Treatment of an Acute Flare of Inflammatory Bowel Disease

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Abstract

***Introduction:** Fecal calprotectin (FC) is a noninvasive biomarker of inflammation used to predict relapse and monitor remission in inflammatory bowel disease (IBD). Physicians currently measure FC values to track patients' inflammatory status. We evaluated how intensive therapy for an acute flare of IBD impacts FC immediately following treatment.*

***Methods:** In a prospective pilot study, we evaluated adults with an IBD flare requiring escalation in therapy. A modified partial Mayo Score for ulcerative colitis (UC) (0-3 stool frequency and 0-3 rectal bleeding, max score = 6) and modified Harvey Bradshaw score for Crohn's disease (CD) (0-2 for pain, diarrhea, fever, fistula, and extra-intestinal manifestations, max score = 10) assessed symptom severity pre- and post-treatment. Initial FC was obtained prior to initiation of therapy and again after acute management of the flare. Escalation in therapy consisted of initiation or increase in steroids, initiation or change in biologics, or surgery. IRB approval was granted and T-tests were used for analyses.*

***Results:** Of the 28 enrolled patients, 23 were hospitalized. Mean age was 39 years and 64% were men. Thirteen (46%) patients had UC and 15 (54%) had CD. In UC, mean FC decreased from 838 µg/g to 523 µg/g over median 9 days. Mean pre-treatment modified Mayo score was 3.82 and mean post-treatment score was 0.64. In CD, mean FC decreased from 815 µg/g to 651 µg/g over median 14 days. Mean pre-treatment modified Harvey Bradshaw score was 4.11 and mean post-treatment score was 1.44. In patients who received surgery (n=4, all with CD), mean FC decreased from 988 µg/g to 401 µg/g over median 23 days. In patients with perianal disease (n=4), mean FC declined from 1154 µg/g to 869 µg/g over median 11 days. In those patients with a decline in FC (16; 8 with UC, 8 with CD), severity of symptoms declined by an average of 2.25 modified Mayo points in UC and 3.0 modified Harvey Bradshaw points in CD.*

***Discussion:** FC rapidly declined in the majority of patients in our study and correlated with improving symptom severity scores. FC declined most significantly in patients undergoing surgery. The average decline in FC was greater in UC patients than in CD patients. FC may be employed as a noninvasive biomarker of response to acute therapy in patients with severe IBD flares.*

Keywords: *fecal calprotectin, IBD flare, biomarkers*

Introduction

Evaluating inflammatory bowel disease (IBD) has traditionally relied on patient symptoms, clinical indices, and endoscopic findings. Serum markers such as C-reactive protein are used to diagnose and track disease activity, but are non-specific to the intestine and can be elevated from concomitant non-gastrointestinal inflammatory conditions [1-3]. More recently, stool markers such as lactoferrin and fecal calprotectin (FC) have emerged as noninvasive biomarkers in inflammatory bowel disease. The benefits of fecal biomarkers include greater diagnostic sensitivity and closer correlation with endoscopic activity [3-6].

Calprotectin specifically is a protein in neutrophils that is highly sensitive in assessing intestinal inflammation. FC levels correlate with radio labeled leukocyte excretion, endoscopic, and histologic assessments of inflammation. FC is stable up to seven days in stool at room temperature, making it practical for collection and analysis [1,2,7-9].

The utility of FC has been established in monitoring disease activity, response to treatment in IBD, and predicting risk of relapse, more so in ulcerative colitis (UC) than in Crohn's disease (CD) [1,2,6]. In CD, it has been used as a marker for mucosal healing after the administration of anti – TNF agents [10]. In UC, normalization of FC after anti – TNF administration has been shown to predict clinical remission, and patients with persistently elevated values were more likely to require colectomy [11,12].

Most studies have evaluated FC as a predictor of response and relapse in patients who are in remission over a course of weeks to months [3,9,13,14]. In this prospective trial, we study the utility of calprotectin as a marker for clinical response in the setting of an acute flare.

Materials and Methods

In this single center prospective pilot study, we enrolled adult patients with an acute IBD flare requiring treatment adjustment. Patients had been diagnosed with IBD based on standard clinical, radiographic, histological and endoscopic criteria. Patients with infection documented by positive Gastrointestinal PCR Panel or Clostridium difficile toxin detection were excluded from the trial.

Patients were enrolled between April 2015 and December 2017. All patients were undergoing treatment either at Columbia University Medical Center or as a patient in an IBD practice.

Once enrolled, demographics and treatment modalities were recorded. Patient symptoms were evaluated using a symptom severity score before and after treatment. For UC, a modified partial Mayo Score was used: episodes of diarrhea and number of bloody bowel movements were each assigned a score from 0 to 3, in order of increasing severity, with a maximum score 6. For CD, a modified Harvey-Bradshaw index was used: pain, diarrhea, fevers, presence of fistula, and presence of extra-intestinal manifestations were each assigned a score from 0 to 2, in order of increasing severity, with a maximum score 10. At termination of the trial, calculation of indices were done to evaluate correlation between FC and symptoms.

Stool calprotectin was obtained before treatment adjustment, and after administration of therapy. The same send-out laboratory (ARUP Laboratory, Salt Lake City, Utah) was used to process all specimens, which were handled in accordance with the laboratory's calprotectin collection recommendations.

Mean and median values were calculated, and t-tests were performed as statistical analyses. A p-value < 0.05 was considered statistically significant.

The Institutional Review Board of Columbia University approved this study, and all patients provided their informed consent.

Results

Twenty-eight patients were enrolled in the study period. Twenty-three required hospitalization for IBD therapy and five were treated as outpatients. The median age was 37 years, 64% were male. Thirteen (46%) had UC and 15 (54%) had CD.

Patient treatments are summarized in Table 1, and included the initiation of vedolizumab, infliximab, cyclosporine, and steroids in the UC patients. In the CD patients, treatment included surgery, antibiotics, infliximab, adalimumab, cyclosporine, and steroids. Patients received a combination of treatments, but notably the UC group was comprised of medical management only, while four CD patients underwent operative treatment.

In the UC patients, initial FC was 838 μg/g, with a mean decline of 315 μg/g to 523 μg/g over median 9 days. Patient symptoms were scored using the modified partial Mayo Score, and initial average score was 3.82. This improved to an average of 0.64 at the time of second FC collection.

For CD patients, mean FC decreased by 164 μg/g, from 815 μg/g to 651 μg/g over median 14 days. Initial modified Harvey-Bradshaw average was 4.11, improving to 1.44 at time of second FC collection.

For patients who underwent surgery (four patients, all with CD), there was a mean decline in FC of 587 μg/g, from 988 μg/g to 401 μg/g over a median of 23 days. In patients with perianal disease (four patients), there was a mean decline in FC of 285 μg/g, from 1154 μg/g to 869 μg/g over a median of 11 days. Table 3 highlights specific FC trends for patients in our study.

Table 1. *Treatments*

Disease	Treatment	No. Patients Receiving Treatment*
UC	Vedolizumab	2
	Infliximab	1
	Cyclosporine	2
	Steroids	6
	5-ASA	5
CD	Surgery	4
	Antibiotics	8
	Infliximab	5
	Cyclosporine	1
	Mercaptopurine	1
	Steroids	7

**Patients often received a combination of treatments*

Discussion

The average FC value declined significantly and rapidly in our patients following management of an acute flare of IBD and correlated with improving symptom severity scores. The most significant decline was in patients who had surgery, a definitive management for medically refractory disease. However, the average time elapsed between FC measurements was longest in this group (median 23 days). Patients with perianal disease (n = 4) also saw a decrease in mean FC. Of note, three of these patients had colonic disease in addition to perianal disease. As FC values decreased in our patients, the average symptom severity score declined as well.

FC has been used to monitor the response to treatment in IBD, and is superior to serum markers and clinical scores in its assessment of endoscopic inflammation [15-17]. Furthermore, it has been a harbinger of clinical activity in a symptomatic IBD patients [12,18,19]. Although FC's response to treatment has been previously evaluated, this was over a longer time period than our study. Specifically, Reinisch et al. found in a study of UC patients FC declined significantly over a 6-week period following induction with Vedolizumab compared to placebo [24]. A study in CD demonstrated a persistent elevation of FC over a 14-week study period was correlated with a primary nonresponse to infliximab therapy compared to those with a decline in FC following treatment [25]. Our study is one of few todemonstrate that FC decreases rapidly (median follow up of 10 days) following acute management of a severe IBD flare.

While there was a statistically significant decline in mean FC, the second value remained elevated. Given the short period to the second collection, complete cellular healing would be unlikely; therefore levels of our second FC were not in the normal range. This is similar to results from a study by Kolho, et al., where fifteen pediatric patients on glucocorticoid therapy had decreased FC within four weeks of steroid therapy.[20].

Our study is limited, most prominently by our small sample size. Our results, while encouraging, should be repeated in larger numbers. Additionally, our parameters for improvement were based on patient symptoms, a bedside approximation of mucosal healing, not endoscopic or histologic findings. However, FC has been shown to correlate with endoscopic evaluation of intestinal inflammation in previous studies [9,13,22,23]. The strengths of this study include the same assay used for all FC measurements, and the rapidity of collection from patient directly to laboratory for analysis. Additionally, the results of this study are widely applicable, to both inpatients and outpatients, over a variety of ages, genders, and disease severity.

Measuring FC could serve as a proxy for endoscopic healing, especially since it is not associated with the cost and procedural risk of an endoscopic procedure [21]. FC is a non-invasive, specific marker that is easy to collect and widely available. Monitoring FC during a severe IBD flare could prevent premature termination of therapy, preventing prolonged, undertreated relapse, which is associated with significant disruption of the

patient's well-being. Our results show that utilizing FC during an acute flare could serve as an adjunct marker of improvement in intestinal inflammation and rapid response to treatment.

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The authors have no competing interests to declare.

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