University of Cincinnati

Date: 4/4/2012

I, Dana Michelle Hines Dykes, hereby submit this original work as part of the requirements for the degree of Master of Science in Clinical and Translational Research.

It is entitled:
Evaluating the use of a new radiographic tool to identify high-risk pediatric Crohn's Disease patients

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This work and its defense approved by:

Committee chair: Erin Nicole Haynes, DrPH

Committee member: Lee Denson, MD

UNIVERSITY OF CINCINNATI

2484
Evaluating the use of a new radiographic tool to identify high-risk pediatric Crohn's Disease patients

A thesis submitted to the
Graduate School
of the University of Cincinnati
in partial fulfillment of the
requirements for the degree of

Master of Science in the program of Clinical and Translational Research
In the Department of Environmental Health
Division of Epidemiology & Biostatistics
of the College of Medicine
May 2012
by

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ABSTRACT

Background. Patients with Crohn’s Disease (CD) and elevated levels of Granulocyte-Macrophage Colony-Stimulating Factor auto-antibodies (GM-CSF Ab) are twice as likely to develop stricture and penetrating behavior requiring surgery. Detection of small bowel lesions such as luminal narrowing with the highly sensitive techniques Computed Tomography and Magnetic Resonance Enterography (CT-E and MR-E) may identify patients prior to developing strictures requiring surgery.

Objective. To determine whether CD patients with high GM-CSF Ab (more than 1.6 mcg/mL) have a higher prevalence of luminal narrowing and complicated disease behavior on CT-E or MR-E.

Methods. A single center, two-phase, cross-sectional study of pediatric patients undergoing both enterography and GM-CSF Ab levels. For the retrospective arm 51 patients with CD were included for analysis, and for the prospective arm, 120 pediatric patients scheduled for CT-E or MR-E. Exams were evaluated for presence or absence of luminal narrowing, stricture (fixed luminal narrowing combined with pre-stenotic dilation and/or fecalization of the proximal small bowel), abscess, or fistulae. Patients underwent GM-CSF Ab testing if no previous value was available. Continuous variables were analyzed using t-test and dichotomous variables using Fisher’s exact test.

Results. Of the 51 retrospective and 65 prospective CD patients, the median GM-CSF Ab was elevated with median (IQR) of 2.35 (0.6, 7.4) mcg/mL and 2.0 (0.5, 6.1) mcg/mL compared with the non-CD healthy/disease control median of 0.6mcg/mL (0.3,1.3), p≤0.009. A previously identified cut-off of 1.6 mcg/mL was used for high vs low antibody for the CD patients. Among CD patients, race, age, and duration of disease were not different by antibody status within each cohort. Duration of disease was longer for the retrospective cohort with an average of 3.5 (3.0) years compared with the prospective patients with an average 2.2 (3.2) years, p≤0.009. The retrospective cohort averaged 21 (6) months of follow-up compared with the prospective 8 (4) months, p=0.02. Paris criteria were not different for age at diagnosis for either cohort. High GM-CSF Ab was associated with an increased prevalence of ileal disease (L1/L3 vs L2) with p<0.005 for both cohorts. Strictureing and/or penetrating behavior was more prevalent in high GM-CSF Ab patients, but this difference was significant only for the prospective cohort, p=0.024. On enterography examination, luminal narrowing was more prevalent for both retrospective and prospective cohorts with p=0.047 and p=0.004. Stricture prevalence was increased for high GM-CSF Ab patients in both cohorts with p=0.05 and 0.01, but there was no difference in penetrating disease outcomes. Of five patients with isolated luminal narrowing at the time of enterography who have progressed to develop stricture, all had high GM-CSF Ab and four also had luminal narrowing on enterography.

Conclusion. Pediatric CD patients with high GM-CSF Ab levels have a higher prevalence of luminal narrowing and strictures and on enterography. Luminal narrowing may progress to strictureing in high risk individuals. Prospective evaluation will be necessary to further evaluate this correlation and to determine whether early infliximab use might reduce progression to strictureing disease and surgery.
ACKNOWLEDGMENTS

Thanks to Dr. Lee “Ted” Denson, Erin Bonkowski, Ben Fey, Mona Bezold, and Katie Lake for their support of this research.

Thanks to my husband for his support every day, no matter what.
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INTRODUCTION

The incidence of Inflammatory Bowel Disease (IBD) in children has doubled over the last two decades to 2.44 cases/100,000 people/year with most new cases being Crohn’s Disease (CD). Patterns of Crohn’s Disease behavior vary by age and are classified by outcomes such as inflammation, stricturing disease (narrowing and blockage of the intestine), and internal penetrating disease (development of fistulae or abscesses). Patients diagnosed during the pediatric period frequently have more aggressive disease and up to 34% of these patients require surgery within 5 years of diagnosis.

The identification of a biomarker for disease progression may help promote targeted screening regimens and treatments for these high-risk individuals. For example, models incorporating existing biomarkers such as ASCA, anti-OMPC, and CBir1 and genetic polymorphisms in genes such as NOD2 have been developed to predict disease behavior. While helpful in some instances, available biomarkers have limitations, particularly in the pediatric IBD population. Biomarkers such as ASCA and pANCA may be absent in 50-70% of children who require early surgery. In addition, biomarker patterns change with age and could limit their utility depending on when they are checked.

Granulocyte-Macrophage Colony-Stimulating Factor autoantibodies (GM-CSF Ab) have been identified as a new biomarker for disease severity in CD which is stable over time and is an independent risk factor for severe Crohn’s Disease behavior. First identified in patients with Primary Alveolar Proteinosis, GM-CSF Ab affects mucosal barrier function and intestinal permeability in mice and in humans. Patients with CD and high GM-CSF Ab typically have ileal disease location and exhibit rapid progression of disease marked by a two-fold higher risk of strictures, penetrating disease, and surgery. While GM-CSF Ab has the benefit of predicting disease behavior in the absence of other biomarkers, the positive predictive value for identifying patients likely to have severe outcomes at 1 year is 21% and 52% at 5 years and is not superior to other existing biomarkers. These data are based on defining stricturing by the less
sensitive radiographic technique small bowel follow through (SBFT), or at the time of surgery after disease has progressed.11

Computed Tomography Enterography (CT-E) has recently replaced SBFT as the new radiographic gold standard for the identification of small bowel disease due to high sensitivities ranging 83-95% compared with SBFT 32-65%.14-16 Enterography also has the capability to detect extra-enteric disease, a feature lacking by SBFT or capsule endoscopy.14-17 While investigations focused on the radiation free alternative Magnetic Resonance Enterography (MR-E) have found similar, though slightly lower sensitivities, available evidence indicates that both modalities should be considered acceptable options for the management of pediatric Crohn’s Disease and have been shown to affect changes in medical management and physician’s assessment of disease activity.15,16,18-20 At our own institution, a recent study of MR-E compared to ileocolonoscopy found a sensitivity of 92-100% for small bowel disease with specificity ranging from 75-100% indicating that MR-E appears to be appropriate for the detection of small bowel disease among CD patients.21

Application of highly sensitive enterography techniques for high-risk CD patients may permit detection of early lesions prior to the development of complications when medications might still be altered. Specifically, patients at risk for stricture such as those with high GM-CSF Ab levels would be potential beneficiaries of the combination of sensitive enterography technique biomarkers for disease behavior. Unfortunately, early predictions of lesions that may progress to stricture have proven difficult since determination of inflammation has been more reproducible than that of fibrosis.22,23 Luminal narrowing, or narrowing of the intestinal lumen without upstream dilation or fecalization suggestive of true stricture, has emerged as a potential feature which may predict future stricture sites and is observed with and without signs of inflammation.24 Patients with luminal narrowing without signs of obstruction have been shown to be more responsive to medical therapy than patients with both luminal narrowing and pre-
stenotic dilation indicative of stricture. Further investigation into this particular lesion would help determine if it is present with greater frequency in patients at highest risk for development of stricture and if these lesions progress to true stricturing disease.

We hypothesized that patients with Crohn’s Disease and elevated GM-CSF auto-antibodies would have a significant increase in the prevalence of luminal narrowing visualized by Computed Tomography Enterography and Magnetic Resonance Enterography. We also hypothesized that these patients would be more likely to progress to stricturing disease.

METHODS

Patients. The Institutional Review Board at Cincinnati Children’s Hospital Medical Center (CCHMC) and the University of Cincinnati (UC) approved this study. In the first arm of the study, a retrospective analysis was performed of an available patient group who had Crohn’s disease, had undergone enterography at some point during their disease course, and had GM-CSF Ab testing available. A second arm was prospectively recruited for a separate analysis. Patient inclusion criteria were (1) age greater than five years, (2) signed parental permission from parents and/or child’s assent if over age 11, (3) clinically indicated CT-E or MR-E. Exclusion criteria included children age five or younger. For both arms, clinical, diagnostic, and demographic data were collected. Patients were consecutively enrolled for the prospective arm regardless of diagnosis.

GM-CSF Ab. Patients underwent blood testing for GM-CSF Ab at the time of enterography if no previously collected sample was available. GM-CSF Ab was measured in serum using enzyme-linked immunosorbent assay (ELISA). The intra-assay coefficient of variation (CV) for the test is 4.3%, while the inter-assay CV is 10.3%. Based upon our previous study of CD patients, risk for aggressive stricturing and penetrating disease increased for
patients in whom the GM-CSF Ab level was greater than the pediatric median value of 1.6 mcg/mL, and this was used as the cut-off for high vs low.\textsuperscript{11}

\textbf{Enterography.} Patients underwent clinically indicated CT-E or MR-E. Standard hospital protocol was used and did not include bowel preparation. Patients did not receive sedation and were required to have nothing by mouth for four hours prior to the procedure. Patients consumed oral contrast one hour before the procedure (VoLumen; Bracco Diagnostics Inc., Princeton, NJ) 20 mL/kg to a maximum dose of 1350 mL over 30 - 45 minutes and followed by 8 oz water. Patients undergoing CT examinations were given a 2ml/kg IV dose of contrast (Opti-ray; Mallinckrodt, Inc., St. Louis, MO). The exam was then performed on a helical CT scanner with 3.0mm slices. The kVp was adjusted by weight. For MRI exams, patients were given a 0.3 mg of glucagon subcutaneously before precontrast images were obtained. Subsequently a second 0.3 mg dose of glucagon was given by slow IV push was given and followed by a 0.1 mmol/kg IV dose of gadolinium. All MR examinations were performed on a 1.5-T MR scanner with an 8-channel phased array body or cardiac coil.

Each test was evaluated by two pediatric radiologists and compared to the clinical radiographic report. Based on agreement with the clinical report, an expert reviewer was chosen for statistical purposes. Enterography features were labeled as present or absent and included luminal narrowing (narrowing of the intestinal lumen only with no signs of obstruction), stricture (narrowing of the lumen with upstream dilation or fecalization), abscess, phlegmon, and internal fistula. Mucosal hyperenhancement and bowel wall thickening were examined for the purposes of choosing an expert reader.

\textbf{Reliability testing.} Kappa values were performed to determine interobserver agreement with respect to key outcomes and were used to determine an expert reader. Three comparisons were made: Reader 1 vs Reader 2, Reader 1 vs clinical report, and Reader 2 vs clinical report.
Strictures were assessed first as one of the primary outcomes. Kappa values were good between Reader 1 and the clinical report with a value of 0.8 (95% CI 0.6-1). Comparisons involving Reviewer 2 were less consistent, with kappa values ranging 0.2-0.3 for stricturing. Interobserver agreement for fistulae and abscesses were very good for all three comparisons with kappa values ranging 0.6-1 but were best for Reader 1 compared with the clinical report with a kappa 0.8 (95% CI 0.6-1) for fistulae and 1 (95% CI 0.5-1) for abscess. Interobserver agreement for luminal narrowing was fair for all three comparisons with values ranging from 0.2-0.5, but again Reader 1 was the best with a kappa of 0.5 against the clinical report. Mucosal hyperenhancement and bowel wall thickening were evaluated as well for purposes of determining an expert reader, since these features are more universally reported than luminal narrowing in the literature and at our institution.\textsuperscript{15,16,19,21,23} Reader 1 and Reader 2 had comparable interobserver agreement for both parameters with kappa values of 0.6-0.7. The overall interobserver agreement was good with an average kappa of 0.4-0.8, but Reader 1 was chosen as the expert reader for purposes of statistical analysis based on overall superior interobserver agreement with kappa of 0.8 compared to the clinical report.

\textit{Statistical analysis.} Statistical analysis was done using SAS version 9.2 (SAS Institute, Inc., Cary, NC) and GraphPad PRISM version 5.03 (GraphPad Inc., San Diego, CA). The retrospective cohort was a convenience group of patients and included all 51 Crohn’s Disease patients at CCHMC who had undergone both GM-CSF Ab testing and a clinically indicated enterography. Power analysis for the prospectively collected cohort was performed using the stricturing rates from the clinical enterography reports of the retrospective cohort. Using the assumption of at least a 2.5 times higher rate of stricturing in high antibody patients from the retrospective cohort, power analysis showed that a sample size of 100 patients with at least 60% of these having CD (based on ordering patterns at CCHMC) would have greater than 80% power with $\alpha=0.05$ to detect a difference in stricturing. In order to allow for patient drop-out or failure to complete all parts of the study, 120 patients were to be enrolled. For both arms of the
study, continuous variables were analyzed using the unpaired t-test and dichotomous variables using Fisher’s exact test. Progression to surgery was evaluated using retrospective analysis of the retrospective cohort, and prospective follow-up of the prospectively recruited cohort.

RESULTS

Patient demographics. The retrospective arm included 51 Crohn’s Disease patients and the prospective arm consecutively enrolled 120 patients. Among the 120 patients enrolled in the prospective arm, 104 completed both enterography and GM-CSF Ab and were included for analysis. Non-completers did not complete the enterography examination based on clinical decision or patient preference. Crohn’s Disease was the most common indication for enterography in the prospective cohort with 65% of patients carrying this diagnosis. Healthy and disease controls were included for initial analyses. Healthy controls with abdominal pain accounted for 21% of the prospectively enrolled patients. The remainder of the patients were disease controls with either Ulcerative Colitis (UC) or Indeterminate Colitis (IC). There was no significant difference in gender, age, or race between the retrospective and prospective CD patients, or the healthy and disease controls (see Table 1). Within each study cohort, the Crohn’s Disease patients were analyzed separately for demographic differences according to antibody status. In the retrospective cohort there was no difference between age, gender, or race, but in the prospective cohort there were slightly more females in the high antibody group (61%) compared with the low antibody group (38%) with $p=0.04$. As expected, the median GM-CSF Ab level for CD patients was significantly elevated compared to non-CD patients, with a median of 2.35 mcg/mL in the retrospective cohort, 2.0mcg/mL in the prospective cohort, and 0.6mcg/mL in the non-CD patients, $p \leq 0.009$ (see Table 1).
GM-CSF Ab and Crohn’s Disease characteristics.

Crohn’s Disease patients were examined with respect to GM-CSF Ab status. Antibody status was categorized as high or low based on previous data showing increased risk of strictures and surgeries for patients with levels over 1.6mcg/mL. The average duration of disease in the retrospective cohort was 3.5 yrs (+/- 3 yrs) while the prospective cohort was significantly shorter with a duration of 2.2yrs (+/- 3.2 yrs), p=0.02 (see Table 1). The retrospective cohort also had longer follow-up after enterography with an average of 21 months (+/- 6 months) compared with 8 months (+/- 4 months) in the prospective cohort, p=0.001. Within each cohort, the duration of disease and follow-up period did not differ between high and low antibody groups (data not shown).

At entrance into the study, patients were classified according to the Paris Classification for categorization of pediatric IBD phenotypes. Using the Paris age groupings by age at diagnosis, the majority of patients were categorized as A1b (age 10 to 17 at diagnosis) with 71% of the retrospective patients and 69% of the prospective cohort falling into this category. There was no difference in age at diagnosis between high and low antibody groups in either cohort (data not shown). As expected, there was a higher rate of ileal disease location in the high antibody patients for both cohorts. As shown in Figure 1, disease location was quite different when stratified by antibody status, with 90% of the retrospective high antibody patients and 92% of the prospective high antibody patients exhibiting ileal disease location compared with 47% and 55% of those with low antibody levels in each cohort. Disease behavior was predominantly complicated stricturing and/or penetrating (Paris criteria B2, B3, or B2/B3) in the high antibody group for both cohorts, but this difference was not significant in the retrospective cohort. The prospectively recruited patients included newly diagnosed patients, and 40% of this cohort had been diagnosed within the last two months with no difference between high and low antibody groups (p=0.15).
Previous medication exposure was examined for each cohort with respect to antibody status. Both cohorts had high rates of exposure to steroids, aminosalicylates, immunomodulators, (methotrexate, 6-mercaptopurine, azathioprine), and anti-TNF agents such as infliximab, with 40-85% of patients having been exposed to each medication. There was no difference in exposure to each medication class when patients were stratified by antibody status with the exception of oral steroids. No difference was seen in steroid use in the retrospective cohort, but among the prospectively recruited patients 65% of the high antibody patients were exposed to steroids compared with 85% of the low antibody group, \( p = 0.03 \). Methotrexate and topical steroids were used infrequently compared to other medications with 8-16% of each cohort being exposed (data not shown).

**GM-CSF Ab and primary outcomes.**

Luminal narrowing on enterography examination was investigated as a potential marker for future stricture sites. Patients with stricturing or penetrating outcomes were not included in analysis of luminal narrowing. Among the retrospective cohort, luminal narrowing was found in 67% of patients with high antibody compared with 24% of patients with low antibody levels, \( p=0.047 \) (see Figure 2). Analysis of patients in the larger prospectively collected cohort found similar rates of luminal narrowing with 76% of high GM-CSF Ab patients having narrowing compared with 36% of patients with low antibody, \( p=0.004 \) (see Figure 2). During the follow-up period which averaged 22 months for the retrospective cohort and 8 months for the prospectively collected cohort, five patients progressed to stricture development. Of these patients, all had high GM-CSF Ab and four (80%) also had luminal narrowing on enterography.

Patients with high GM-CSF Ab in both retrospective and prospective cohorts had a higher rate of complicated disease behavior at time of enterography. Strictures were found with increased prevalence in both cohorts, with 24% of the retrospective high antibody cohort and
20% of the prospective cohort having strictures at the time of enterography (see Figure 3). Progression to surgery after enterography was more common among high antibody patients in both retrospective and prospective cohorts. Surgery after enterography occurred in 24% of the retrospective high antibody patients and 25% of the prospective high antibody patients, compared with 5% and 7% of the low antibody patients in each cohort, p=0.05 and p=0.04 (see Figure 3). Two newly diagnosed patients in the prospective cohort had strictures at diagnosis and both had high GM-CSF Ab levels while none of the low antibody patients had strictures at diagnosis. Internal penetrating disease alone or combination stricturing/penetrating disease at the time of enterography was not significantly different between high and low GM-CSF antibody groups for either cohort (see Figure 4).

DISCUSSION

Previous studies have shown that biomarkers, including GM-CSF Ab may be used to identify CD patients at risk for severe progressive disease and have been used to develop risk predication models incorporating potential treatment algorithms.\textsuperscript{7,8,11} In an effort to improve the use of these biomarkers to predict disease behavior, we present the first study to combine a biomarker, GM-CSF Ab, with a sensitive radiographic technique in order to guide future efforts to target these high-risk individuals for more aggressive screening or medications earlier in disease course.

We proposed that luminal narrowing on enterography may suggest sites of early stricture formation. The results of both retrospective and prospectively collected cohorts confirmed a significantly higher rate of luminal narrowing in patients with high GM-CSF Ab levels. While the numbers are small and followed for relatively short time period after enterography, 80\% (4/5) of the patients who did not have stricture or other complicated disease behavior at study entrance who progressed to true stricture had both luminal narrowing on enterography and high GM-CSF Ab. The only patient who progressed and did not have luminal narrowing at the time of
enterography had high GM-CSF Ab alone. While this study was not powered sufficiently to determine if this progression to stricture is significant, these findings suggest that luminal narrowing and progression to stricture warrants further investigation in this high-risk group.

While prospective evaluation of luminal narrowing as a risk for progression to future stricturing is not described in the literature, this data serves as a first step to identify enterography features which may help improve the identification of early stricture sites in high-risk patients. The presence of both luminal narrowing and pre-stenotic dilation, or “hold-up,” on enterography examination has been used as the strict radiographic definition of stricture. Using these criteria, enterography has been shown to accurately identify strictures and is better than physician assessment to determine the presence of true stricture. Patients with both luminal narrowing and “hold-up” (or pre-stenotic dilation) are less likely to respond to medical therapy than patients with luminal narrowing alone. As shown in the small number of patients in this study, these areas of luminal narrowing may progress to future stricture development. Future studies will be necessary to determine if early treatment with medications such as infliximab may prevent progression to true stricture.

The secondary outcome of this study was to confirm that enterography would identify a higher prevalence of complicated disease behavior. While we found a significant increase in both the prevalence of strictures and progression to surgery during follow-up for both cohorts, the prevalence of penetrating outcomes was not significantly different. This study was not powered to detect a difference in penetrating complications, but the failure to identify a difference in this outcome may represent a clinically important observation. In the initial cohort published by Han et al, patients were not stratified by separately by stricturing or penetrating behavior but instead were analyzed together. Further analyses of larger prospective cohorts may help define if the presence of GM-CSF Ab increases the risk for stricturing alone, or if these findings resulted from underpowering.
While cross-sectional in nature, both cohorts replicated the expected phenotype of patients with high versus low GM-CSF Ab. The increased prevalence of ileal disease location (L1/L3) and early complicated disease behavior (B2, B3, or B2B3) for individuals with high GM-CSF Ab confirm the findings in the original prospective cohort.\textsuperscript{11} While the prevalence of complicated disease behavior was not statistically different by antibody status in the retrospective cohort, these patients had a longer disease duration which may have affected the number of disease complications, since the risk of complications increases with time after diagnosis.\textsuperscript{3,6} The prospectively recruited cohort, on the other hand, had a much shorter duration of disease (around 2.2 years), and 47% of the patients had already had a severe disease complication at study entry. This recapitulates the relevance of GM-CSF Ab as a risk factor for early complicated disease behavior.

Although the results of this study suggest important implications for the combination of sensitive radiographic techniques with existing biomarkers, this study did have some unique strengths and limitations. Our institution has the benefit of being both a regional referral center as well as a large quaternary medical center, so the results should be generalizable to other patients with CD. Other strengths include highly experienced radiologists with a special interest in using enterography for pediatric patients. Previous studies have found fair to good interobserver agreement for both CT-E and MR-E with kappa values ranging 0.3-0.9 for most parameters.\textsuperscript{15,16,19,28} A recently published study at our own institution found interobserver agreement to be good with kappa of 0.59.\textsuperscript{21} Our average kappa values ranged 0.4-0.8 by parameter and suggest moderate to good interobserver agreement. The inclusion of the clinical report as a “third reviewer” was a strength of the study and allowed introduction of a report from individuals without a special interest in IBD imaging and helps assure generalizability of results to other institutions. A potential limitation of this study is the use of both CT-E and MR-E for analysis, but since previous studies have shown similar sensitivities, specificities, and intermodality agreement between the two techniques, we felt that this study would provide valid
results representative of clinical practice in which both techniques will be utilized.28 The cross-sectional nature of both arms of the study is a slight limitation in that patients entered the study at varying stages of disease. Nonetheless, the similar results between cohorts despite differences in disease duration and follow-up suggest that the findings of this study are reproducible. While a true prospective study would determine with more certainty the prevalence of luminal narrowing and the progression to stricture in patients with high GM-CSF Ab using enterography, this data will facilitate future studies aimed at earlier identification of complications and medication response in this vulnerable population.

This is the first effort to correlate enterography findings with biomarker status. Future studies may help further characterize luminal narrowing as a predictor of stricturing behavior in high-risk individuals. Studies aimed at evaluation of medication response and timing of progression to surgery will provide more information about these lesions and the implication for use in clinical care. Ultimately, the incorporation of GM-CSF Ab data into existing risk prediction models may provide additional benefit for patients with CD.
Table 1: **Demographic Features of Patients at Enrollment**

<table>
<thead>
<tr>
<th></th>
<th>Retrospective Crohn’s (n=51)</th>
<th>Prospective Crohn’s (n=65)</th>
<th>Healthy and Disease Controls (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years (SD)</strong></td>
<td>15.1 (3.6)</td>
<td>14.9 (7.1)</td>
<td>13.9 (3.6)</td>
</tr>
<tr>
<td><strong>Females. n (%)</strong></td>
<td>26 (51%)</td>
<td>33 (51%)</td>
<td>18 (46%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cauc (n,%)</td>
<td>49 (96%)</td>
<td>56 (86%)</td>
<td>34 (87%)</td>
</tr>
<tr>
<td>AA (n,%)</td>
<td>1 (2%)</td>
<td>7 (11%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Other (n,%)</td>
<td>2 (2%)</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>GM-CSF Ab, median (IQR)</strong></td>
<td>2.35 (0.6,7.4)</td>
<td>2.0 (0.5,6.1)</td>
<td>0.6* (0.3,1.3)</td>
</tr>
<tr>
<td><strong>Disease duration, years</strong></td>
<td>3.5 (3.0)</td>
<td>2.2 (3.2)**</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Follow-up, months (SD)</strong></td>
<td>21 (6)</td>
<td>8 (4)*</td>
<td>n/a</td>
</tr>
</tbody>
</table>

*indicates significance with p ≤0.009, **Indicates significance with p=0.02, all others not significant.
Figure 2: Paris criteria (Location and Behavior) for Crohn’s Disease Patients. Retro=Retrospective CD patients, Prosp=Propsective CD Patients, Complicated behavior=B2,B3, or B2B3. *Indicates p=0.02, **Indicates p<0.005.

Figure 2: Luminal narrowing by GM-CSF Ab status. A) Retrospective cohort, p=0.047. B) Prospective cohort, p=0.004
Figure 3: Stricturing and surgery by GM-CSF Ab status. A) Retrospective cohort, frequency of stricturing by antibody status, p=0.05. B) Prospective cohort, frequency of stricturing by antibody status, p=0.01. C) Retrospective cohort, frequency of surgery after enterography by antibody status, p=0.05. D) Prospective cohort, frequency of surgery after enterography by antibody status, p=0.04.
Figure 4: Complicated behavior (stricturing alone, combination stricture and penetrating disease, or penetrating disease alone) by antibody status. Only stricturing was significantly different between antibody groups. A) Retrospective cohort, B) Prospective cohort.