HHS Public Access

Author manuscript

Am J Gastroenterol. Author manuscript; available in PMC 2019 December 31.

Published in final edited form as:

Am J Gastroenterol. 2010 May ; 105(5): 1133–1139. doi:10.1038/ajg.2010.9.

Clinical Utility of Measuring Infliximab and Human Anti-Chimeric Antibody Concentrations in Patients With Inflammatory Bowel Disease

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Abstract

OBJECTIVES: Human anti-chimeric antibodies (HACAs) and subtherapeutic infliximab concentrations are associated with decreased duration of response. We evaluated the clinical utility of measuring HACA and infliximab concentrations.

METHODS: The medical records of patients with inflammatory bowel disease (IBD) who had HACA and infliximab concentrations measured were reviewed to determine whether the result affected clinical management.

RESULTS: One hundred fifty-five patients had HACA and infliximab concentrations measured. The main indications for testing were loss of response to infliximab (49%), partial response after initiation of infliximab (22%), and possible autoimmune/delayed hypersensitivity reaction (10%). HACAs were identified in 35 patients (23%) and therapeutic infliximab concentrations in 51 patients (33%). Of 177 tests assessed, the results impacted treatment decisions in 73%. In HACA-positive patients, change to another anti-tumor necrosis factor (TNF) agent was associated with a complete or partial response in 92% of patients, whereas dose escalation had a response of 17%. In patients with subtherapeutic infliximab concentrations, dose escalation was associated with complete or partial clinical response in 86% of patients, whereas changing to another anti-TNF agent had a response of 33%. Patients with clinical symptoms and therapeutic infliximab concentrations were continued at the same dose 76% of the time and had no evidence of active inflammation by endoscopic/radiographic assessment 62% of the time.

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Specific author contributions: Study design, data collection, statistical analysis, and writing of the draft manuscript: Waqqas Afif; study design, data collection, statistical analysis, and critical revision of the manuscript: Edward Loft us; data collection and critical revision of the manuscript: William Faubion; data collection and critical revision of the manuscript: Sunanda Kane; data collection and critical revision of the manuscript: David Bruining; data collection: Karen Hanson; study design, data collection, statistical analysis, and critical revision of the paper: William Sandborn. All authors approved the final submission.

CONFLICT OF INTEREST

Guarantor of the article: Waqqas Afif, MD.

Potential competing interests: William Sandborn is a consultant to and has received research support from Centocor, Schering-Plough, Abbott Laboratories, and UCB Pharma. Edward Loft us has received research support from Schering-Plough and has participated in continuing medical education activities sponsored in part by Centocor. William Faubion is a consultant to and has received research support from Centocor and Abbot Laboratories. Dr Kane is a consultant to Abbott Laboratories.

CONCLUSIONS: Measurement of HACA and infliximab concentration impacts management and is clinically useful. Increasing the infliximab dose in patients who have HACAs is ineffective, whereas in patients with subtherapeutic infliximab concentrations, this strategy may be a good alternative to changing to another anti-TNF agent.

INTRODUCTION

Infliximab (Remicade, Centocor, Horsham, PA) is a chimeric monoclonal IgG1 antibody against tumor necrosis factor (TNF) that is effective for the treatment of Crohn's disease and ulcerative colitis (1–3). Treatment with infliximab can result in immunogenicity and the formation of human anti-chimeric antibodies (HACAs), also known as antibodies to infliximab (4). The incidence of HACAs has been shown to be as high as 37–61% in patients receiving episodic infliximab (4). Scheduled infliximab therapy decreases the incidence of HACAs to 6–16 % (2,5). Concomitant immunosuppressive therapy also decreases the formation of HACAs, but this may only be important in those receiving episodic therapy (2,4–9). Immunogenicity to infliximab is not a unique phenomenon related to its chimeric structure, as treatment with any exogenous protein can lead to the development of antibodies (10,11). In fact, similar rates of antibodies have been reported in patients treated with adalimumab and certolizumab pegol (12–15).

Some have questioned whether the presence of antibodies to anti-TNF agents directly correlates with decreased efficacy (16). Comparisons can be drawn from the rheumatoid arthritis literature. Several groups have shown that the development of antibodies to infliximab and adalimumab correlates with not only decreased drug concentrations but also decreased clinical response (17–21). In inflammatory bowel disease (IBD), studies have shown that there is a shorter duration of clinical response in patients with detectable HACA concentrations (4,22,23). A subgroup analysis of a larger randomized controlled trial showed a trend toward decreased remission in patients who underwent episodic therapy and had detectable antibodies (6).

The clinical efficacy of infliximab may be dependent not only on the absence of HACA but also on infliximab concentrations. In a study of Crohn's disease patients on scheduled maintenance infliximab therapy, patients with detectable trough concentrations had a higher rate of clinical remission, a lower serum C-reactive protein (CRP) concentration, and a higher rate of endoscopic improvement (5). HACAs have also been associated with an increased risk of infusion reactions, which in turn can also lead to decreased infliximab concentrations (4–6,23,24).

Although the associations between clinical efficacy and infusion reactions with infliximab concentrations and HACA status have been described, the clinical utility of these tests in routine practice remains unclear. The clinical indications for measuring HACA and infliximab concentrations in patients with IBD have not been previously assessed. Furthermore, the optimal patient management based on the results of testing has not been clearly elucidated. We retrospectively studied the utility of measuring HACA and infliximab concentrations and compared subsequent clinical management and response. We propose a treatment algorithm based on the results of testing.

METHODS

Overview

We conducted a retrospective review of the medical records of all patients at our institution who underwent HACA and infliximab concentration testing. No systematic strategy was used to test all patients who were failing or who were intolerant to infliximab. Physicians working in the Inflammatory Bowel Disease Clinic at Mayo Clinic, Rochester can, at their discretion, order HACA and infliximab concentrations as a send-out test from Mayo Medical Laboratories to Prometheus Laboratories (San Diego, CA). Medical records were electronically searched to identify patients who had received infliximab and who underwent testing for HACA and infliximab concentrations between 1 January 2003 and 1 August 2008. All patients included in the analysis had provided authorization for medical record review for research purposes, and the study was approved by the Mayo Clinic Institutional Review Board.

Inclusion and exclusion criteria

All patients with a diagnosis of Crohn's disease, ulcerative colitis, or indeterminate colitis who were treated with infliximab and underwent HACA and infliximab concentration testing were included in the study. Exclusion criteria were limited to: the absence of follow-up after being tested, and the infusion of infliximab as a part of a clinical trial.

Measures and analyses

Demographic and clinical characteristics were abstracted from the electronic medical record in those patients that met entry criteria. Characteristics included age, gender, smoking status, type of IBD, anatomic distribution, duration of disease, previous surgery, prior and concurrent treatment for IBD, date of infliximab initiation, dose, duration of treatment, clinical response, change in dose or frequency, acute or delayed hypersensitivity reactions, autoimmune reactions, and change to another anti-TNF agent. Acute infusion reactions were defined as an adverse event that occurred within 1 h after infusion. Delayed hypersensitivity reactions were defined as the occurrence of myalgias, arthralgias, fever, or rash occurring 1–14 days after infusion. Clinical response was retrospectively determined as defined earlier (25). In patients with Crohn's disease, complete response was defined as cessation of diarrhea and abdominal cramping, or, in the cases of patients with fistulas, cessation of fistula drainage and complete closure of all draining fistulas. Partial response was defined as a reduction in the amount of diarrhea and abdominal cramping, or, in the case of fistula patients, a decrease in the drainage, size, or number of fistulas. Outcomes not meeting one of the above definitions were classified as non-response (25). In patients with ulcerative colitis, complete response was defined as cessation of diarrhea, hematochezia, and abdominal cramping whereas partial response was defined as a reduction in the amount of diarrhea, hematochezia, and abdominal cramping. The results of radiological and/or endoscopic imaging were documented when available.

The testing date, the reason for testing, and the rationale for changing treatment post-testing were obtained from the medical record. Results of HACA and infliximab concentration testing from Prometheus Laboratories were categorized in the following manner. Infliximab

concentrations ≥ 12 mcg/ml at 4 weeks after infusion were considered therapeutic (4). Patients with a detectable infliximab concentration (> 1.4 mcg/ml) at dosing trough were considered to have therapeutic concentrations (5). Patients with any detectable HACA concentration were considered to have a positive antibody status and by definition, had an undetectable infliximab concentration (the presence of infliximab in the sample interferes with the HACA assay).

Subtherapeutic infliximab concentrations were defined as an undetectable trough concentration or an infliximab concentration < 12 mcg/ml at 4 weeks after infusion. Testing results that were non-interpretable because testing was performed at an inappropriate time were not included in the analysis (e.g., infliximab concentration > 12 mcg/ml before 4 weeks or < 12 mcg/ml after 4 weeks, but before trough dosing). Clinical response (as defined above) to any change in therapeutic treatment was also assessed. C-reactive protein and erythrocyte sedimentation rate at initiation of infliximab, before change in treatment, and post-treatment were abstracted when data were available.

The clinical utility of testing was assessed retrospectively. *A priori*, we determined that when the results of testing changed treatment or helped to avoid inappropriate clinical management, the test was considered useful. Testing was considered to have no impact on clinical decision making when a counterintuitive treatment plan was instituted, for example, when the treating clinicians: dose-increased infliximab when HACAs were detected, maintained the same therapy when subtherapeutic infliximab concentrations were found and either dose-increased infliximab or changed anti-TNF agents when therapeutic infliximab concentrations were detected.

Statistical analysis

Descriptive statistics were used to analyze baseline characteristics. Fisher's exact test, χ^2 test, and log-rank test for discontinuation were used for statistical analysis between groups. A P value of 0.05 was considered significant. Statistical analyses were conducted using Statistical Analysis Software (SAS).

RESULTS

Patient characteristics

One hundred fifty-five patients underwent HACA and infliximab concentration testing between 1 January 2003 and 1 August 2008. One hundred twelve patients (71.8%) of the initial tests were ordered by a single physician (W.J.S.). The baseline demographic and clinical characteristics are shown in Table 1. One hundred twenty-seven patients (82%) received induction followed by scheduled dosing. Among the 28 patients who did not receive induction dosing, 18 (64%) subsequently received scheduled dosing. Forty-seven percent of patients were on concurrent immunosuppressant medication consisting of azathioprine, 6-mercaptopurine, or methotrexate. The median time to initial testing after infliximab initiation was 50 weeks (interquartile ratio [IQR]: 22.7–120), and the median number of infusions (per patient) before testing was 8 (IQR: 4–15). Initial complete clinical response to infliximab therapy was seen in 100 patients (65%), partial response was

observed in 45 patients (29%), and no response was seen in 10 patients (6%). Forty-three patients (28%) had the dose or frequency of infliximab increased before testing. The results of testing stratified by the presence or absence of concomitant immunosuppressive therapy are summarized in Table 2. Concurrent immunosuppressive therapy was significantly associated with negative HACA status (14% in those on concomitant immunosuppressive therapy vs. 29% in those not, $P < 0.032$), as well as therapeutic infliximab concentrations (48% vs. 21%, $P < 0.001$). HACA status did not significantly differ in patients receiving scheduled dosing compared with episodic treatment, but only 10 patients (6%) were receiving episodic treatment.

Indications for testing

The indications for testing are listed in Table 3. The main indications for initial testing were: loss of response to infliximab (49%), partial response after initiation of infliximab (22%), and possible autoimmune/delayed hypersensitivity reaction (10%). HACAs were identified in 35 patients (23%), therapeutic infliximab concentrations were found in 51 patients (33%), and subtherapeutic concentrations were found in 69 patients (44%). Out of the initial 155 tests, only 6 (4%) could not be assessed because they were completed at an inappropriate time leading to non-interpretable results. The results of testing stratified by indication are summarized in Table 4. Out of 110 patients tested for loss of response or partial response, 19 (17%) had detectable HACAs and 50 (45%) had non-therapeutic concentrations. Out of 16 patients tested for autoimmune/delayed hypersensitivity reactions, 6 (38%) had detectable HACAs and in 5 patients tested for an allergic reaction to infliximab, only 1 patient (20%) had detectable HACAs.

Clinical management based on HACA and infliximab concentrations

Of 177 total tests assessed (including 22 subsequent HACA status and infliximab concentration testing), the results impacted treatment decisions as defined above in 130 clinical situations (73%; 95% CI: 66–79%). The clinical scenarios where testing had no impact on clinical management are shown in Table 5.

Thirty-five patients were positive for HACAs. Among the 12 HACA-positive patients who changed to another anti-TNF agent, a complete or partial response was noted in 11 (92%) (Table 6). On the other hand, increasing the dose of infliximab in 6 HACA-positive patients was associated with response in 1 patient (17%, $P < 0.004$). During subsequent testing, none of these patients achieved therapeutic infliximab concentrations with dose escalation. Of the remaining patients, six discontinued infliximab, three continued on the same dose, three proceeded to surgery, and five patients could not be assessed as adequate follow-up information was not available.

Sixty-three patients had subtherapeutic infliximab concentrations. Among 29 patients with subtherapeutic infliximab concentrations, increasing the infliximab dose was associated with complete or partial clinical response in 25 (86%). Six patients with subtherapeutic infliximab concentrations were changed to another anti-TNF, and this was associated with a response in two patients (33%, $P < 0.016$). Of the remaining patients, 10 continued on the

same dose, 9 discontinued infliximab, 8 proceeded to surgery, and 7 patients could not be assessed as adequate follow-up information was not available.

Fifty-one patients had therapeutic infliximab concentrations. In 21 situations where patients had clinical symptoms and therapeutic infliximab concentrations, and radiological and/or endoscopic imaging was available, patients had no evidence of active inflammation 62% of the time (95% CI: 38–82%), and continued at the same dose 76% (95% CI: 54–90%). In the eight patients (38%) that had active inflammation despite therapeutic infliximab concentrations, three patients continued on the same dose, two patients had surgery, two patients were changed to another anti-TNF (no follow-up information available), and one was treated with an additional immunosuppressive agent.

In 5 patients evaluated for acute infusion reactions, 1 patient (20%; 95% CI: 2–64%) had detectable HACAs, whereas among 16 patients assessed for delayed hypersensitivity or autoimmune reactions, 6 had detectable antibody concentrations (38%; 95% CI: 18–61 %). In the seven patients assessed before possible reintroduction of infliximab after a drug holiday, six patients (86%) had detectable HACAs.

Infliximab discontinuation

By the end of the study period (August 2008), among 140 patients with available information, 51 were still on infliximab (36%; 95% CI: 29%–45). The main indications for infliximab discontinuation were loss of response in 38 patients (27%; 95% CI: 20–35%) and continued partial response in 20 (14%; 95% CI: 9–21%). Other indications for infliximab discontinuation (all < 10%) were primary non-response, surgical intervention, autoimmune or delayed hypersensitivity reaction, infusion reactions, or other side-effects. In patients with therapeutic infliximab concentrations who continued the same dose and those with subtherapeutic concentrations who were dose escalated, the median time to discontinuation of infliximab after the test date was similar at 75 weeks (IQR: 46–116 and 45–92, respectively, $P > 0.61$).

DISCUSSION

Infliximab has become a common treatment for both Crohn’s disease and ulcerative colitis. Among patients who initially respond to infliximab, up to 40% will subsequently lose response (2). The clinical management of patients who respond to infliximab and then lose response remains largely empiric. Management strategies include escalation of the dose or shortening of the infusion interval, switching to another anti-TNF agent, or switching to another therapeutic class (26–29). A decision analysis suggested that dose escalation was more likely to be effective than switching drugs within the class, but this empiric strategy likely leads to dose escalation in some patients who are HACA positive (30). It is logical that the incorporation of routine measurement of HACA and infliximab concentrations could lead to a more nuanced approach, but the use of these tests in clinical practice has not been reported.

Our study shows that measurement of HACA and infliximab concentrations is useful in clinical practice. The patients in our study were tested, on average, approximately 1 year

after the initiation of infliximab. The majority of tests were performed for loss of response or partial clinical response (71%) and in these patients 62% had detectable HACAs or non-therapeutic infliximab concentrations. It is in this cohort of patients that the test results are most important in determining appropriate treatment. When ordering HACA and infliximab concentrations, there are three possible permutations (Figure 1).

The presence of HACAs provides clear evidence that immunogenicity to infliximab has developed and that further treatment would result in a decreased clinical response or possible infusion reactions (4–6,16,22,23). Similar to the study by Maser *et al.* (5), patients with any detectable HACA concentration were considered to have a positive antibody status because they likely have developed some degree of immunogenicity to infliximab. In our study, a change to another anti-TNF agent in HACA-positive patients was associated with a complete or partial response in 92%, whereas increasing the dose of infliximab resulted in a 17% response ($P < 0.004$). This would suggest that increasing the infliximab dose in the face of positive HACA is unlikely to be a successful strategy, and the results of HACA testing are indeed useful in this cohort of patients.

In patients with subtherapeutic concentrations, infliximab dose escalation was associated with a significantly increased clinical response compared with changing to another anti-TNF (86% vs. 33%, $P < 0.016$). In addition, patients with therapeutic infliximab concentrations who continued the same dose and those with subtherapeutic concentrations who were dose escalated had a similar median time to infliximab discontinuation (75 weeks). These results suggest that increasing the infliximab dose may be a successful strategy in treating patients with subtherapeutic concentrations. At present, there are no comparative effectiveness studies assessing dose escalation vs. changing to another anti-TNF agent, in patients that lose response to infliximab. Previous exposure to an anti-TNF agent is associated with a reduced clinical response to a second anti-TNF agent compared with anti-TNF naive patients and this could perhaps explain the increased clinical response rate seen with dose intensification in our study (31). Both strategies are likely effective and further studies need to be performed to determine whether one treatment strategy is superior to the other.

A 4-week post-infusion infliximab concentration of > 12 mcg/ml and a detectable trough concentration have both been found to be significantly associated with decreased infusion reactions, increased clinical remission, lower C-reactive protein, and endoscopic healing (4,5). In the presence of therapeutic infliximab concentrations and clinical symptoms, confirmatory testing with ileocolonoscopy and/or computed tomography or magnetic resonance imaging enterography should be performed. To underscore this recommendation, in patients with clinical symptoms and a therapeutic infliximab concentration, patients continued at the same dose 76% of the time and had no evidence of active inflammation by endoscopic/radiographic assessment 62% of the time. Increasing the dose or changing to another anti-TNF agent in these patients would have led to inappropriate management. If therapeutic infliximab concentrations are present and there is persistent disease, then increasing the dose of infliximab or changing to another anti-TNF with the same mechanism of action would likely be of little benefit, and consideration should be given to switching to a medication with a different mechanism of action. In this cohort of patients, infliximab

concentration testing would be clinically useful and would help to avoid inappropriate management.

Although 10 % of HACA and infliximab concentration testing was completed to assess for delayed hypersensitivity reactions (HACAs detected in only 38% of patients), there is little data to support a link between antibody presence and these reactions. In the study by Baert *et al.* (4), there was no relationship between delayed hypersensitivity reactions and HACA concentrations. On the other hand, testing before retreatment with infliximab may be more useful as HACAs were detectable in 86% of these patients in our study. Similarly, in a study published in abstract form, all patients with Crohn's disease who were retreated with infliximab after a drug holiday and developed a delayed hypersensitivity reaction had detectable HACAs after infusion (32).

Patients receiving concurrent immunosuppressive therapy were significantly more likely to have therapeutic infliximab concentrations and less likely to have detectable antibodies, as compared with those not receiving concomitant immunosuppressive therapy. These results should be interpreted with caution given that this is a retrospective study. There are also several other potential limitations to this study. Patient selection for testing was at the discretion of the treating physician, and the resultant cohort of patients represent only a small subset of the total population of patients on infliximab at Mayo Clinic. Clinical response was abstracted through review of patient charts using pre-defined clinical criteria. Validated instruments such as the Crohn's Disease Activity Index, Harvey-Bradshaw Index, and endoscopic improvement could not be obtained retrospectively. In addition, there is no specific comparator/control group in which no testing was performed and so absolute conclusions regarding the superiority of testing over clinical judgment alone cannot be made. However, the results of this study do suggest that testing in specific circumstances could potentially help to avoid inappropriate management.

In conclusion, our data suggest that HACA and infliximab concentration testing impact treatment decisions in 73% of patients and that these tests are a useful adjunct to clinical and endoscopic/radiological assessment. Use of these tests can potentially avoid inappropriate management and optimize patient treatment algorithms (Figure 1). A prospective randomized trial should be conducted to confirm these findings.

ACKNOWLEDGMENTS

The project described was supported by grant number 1 UL1 RR024150 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and the NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- Therapeutic infliximab concentrations likely correlate with increased clinical response, whereas detectable human anti-chimeric antibody (HACA) concentrations may result in decreased clinical efficacy.
- The clinical utility of measuring infliximab and HACA concentrations in routine practice remains unclear, and the optimal patient management based on the results of testing has not been clearly elucidated.

WHAT IS NEW HERE

- In our study, patients with detectable human anti-chimeric antibodies (HACAs) who changed to another anti-tumor necrosis factor (TNF) agent had a significantly increased response compared with patients who were dose escalated.
- Patients with subtherapeutic infliximab concentrations had a significantly increased response when they were dose escalated compared with changing to another anti-TNF agent.
- In the presence of therapeutic infliximab concentrations and clinical symptoms, confirmatory testing with ileocolonoscopy and/or computed tomography or magnetic resonance imaging enterography should be performed before changes in treatment.
- Incorporation of routine measurement of HACA andinfliximab concentrations is clinically useful and may help to optimize patient treatment algorithms.

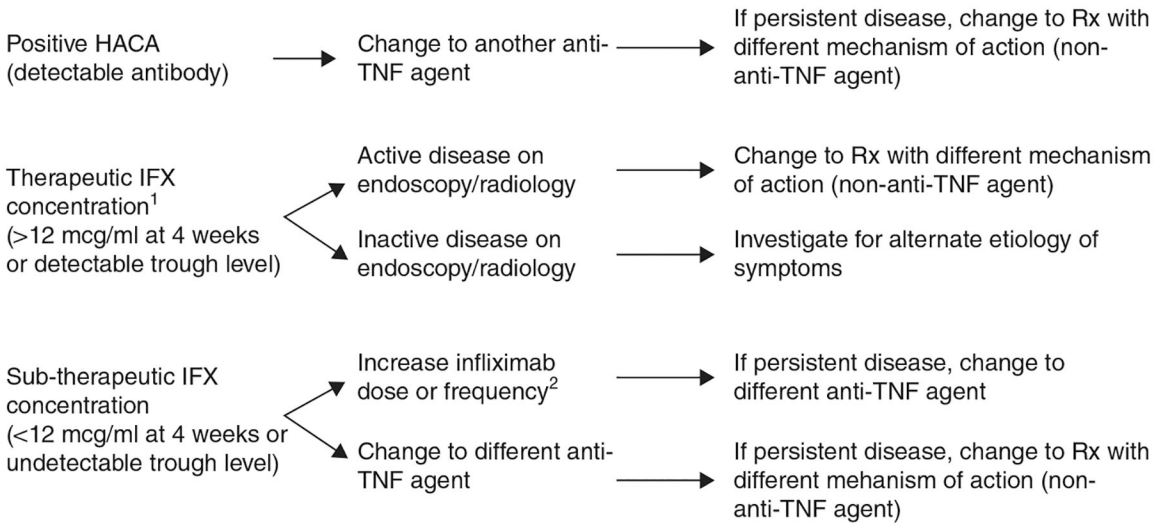

Figure 1.

Treatment algorithm in patients with clinical symptoms (infliximab and HACA concentrations). [1]Patients should save endoscopic or radiologic imaging. [2]This strategy may be preferable. HACA, human anti-chimeric antibody; TNF, tumor necrosis factor.

Table 1.

Baseline characteristics of inflammatory bowel disease patients who underwent testing for human anti-chimeric antibodies and infliximab concentrations

Characteristic	***N* =155**
Females, *n* (%)	86 (55%)
Median age at diagnosis of inflammatory bowel disease (IQR)	25 (18–36)
Median age at time of initial test, years (IQR)	39 (26–50)
Smoking status, n (%)	
Current	82 (21%)
Former (> 1 month with no smoking)	24 (15%)
Crohn's disease	121 (78%)
Ileal	19 (16%)
Colonic only	35 (29%)
Ileocolonic	67 (55%)
Perianal disease	29 (24%)
Surgical management before anti-TNF	65 (54%)
Ulcerative colitis	31 (20%)
Left-sided disease	7 (23%)
Pan-colonic disease	24 (77%)
Indeterminate colitis	3 (2%)
Concomitant medication (at the time of initial test)	
Mesalamine	11 (7%)
Corticosteroids (> 20 mg/day)	16 (10%)
Azathioprine/6-merca ptopuri ne	57 (37%)
Methotrexate	12 (10%)
Induction dosing (0, 2, 6 weeks)	127 (82%)
History of steroid pretreatment	16 (10%)
Initial response to infliximab	
Complete response	100 (65%)
Partial response	45 (29%)
No response	10 (6%)
Median time to initial testing after infliximab initiation, weeks (IQR)	50 (22.7–120)
Median number of infusions (per patient) before test (IQR)	8 (4–15)

IQR, interquartile range; TNF, tumor necrosis factor.

Table 2.

Testing results stratified by concomitant immunosuppressive therapy

	HACAs	Therapeutic IFX	Non-therapeutic IFX	Non-interpretable
Concurrent IS (*n*=69)	10 (14)	33 (48)	22 (32)	4 (6)
No concurrent IS (*n*=86)	25 (29)	18 (21)	41 (48)	2 (2)

HACAs, human anti-chimeric antibodies; IFX, infliximab; IS, immunosuppressive therapy.

Table 3.

Primary indication for testing for human anti-chimeric antibodies and infliximab concentrations

Indication, *n* (%)	***N* =155**
Loss of response	76 (49)
Partial response on initiation	34 (22)
Autoimmune/delayed hypersensitivity reaction	16 (10)
Primary non-response	8 (5)
Reintroduction after drug holiday	7 (5)
Endoscopic/CTE recurrence	6 (4)
Acute infusion reaction	5 (3)
Unclear reason	3 (2)

CTE, computed tomography enterography.

Table 4.

Testing results stratified by indication

	HACAs	Therapeutic IFX	Non-therapeutic IFX	Non-interpretable
Loss of response/partial response (*n*=110)	19 (17)	36 (33)	50 (45)	5 (5)
Autoimmune/delayed hypersensitivity reactions (*n*=16)	6 (38)	5 (31)	4 (25)	1 (6)
Acute infusion reaction (*n*=5)	1 (20)	3 (60)	1 (20)	
Reintroduction after drug holiday (*n*=7)	6 (86)	1 (14)		

HACAs, human anti-chimeric antibodies; IFX, infliximab.

Table 5.

Scenarios in which testing did not impact clinical management

	Clinical management	***n* = 47**
Detectable HACA	Increase infliximab	7
	Continue infliximab	4
Therapeutic concentrations	Change to another anti-TNF	10
	Increase infliximab	2
	Continue infliximab despite endoscopic/CTE recurrence	3
Subtherapeutic concentrations	Continue infliximab (same dose)	15
	Change treatment secondary to adverse events[a]	6

CTE, computed tomography enterography; HACA, human anti-chimeric antibody; TNF, tumor necrosis factor.

[a]These included delayed hypersensitivity reactions ($n = 4$), tuberculosis ($n = 1$), and lymphoma ($n = 1$).

Table 6.

Clinical outcomes of patients with detectable human anti-chimeric antibodies or subtherapeutic infliximab concentrations

	Response to test	Complete/partial response (%)	*P* value
Detectable HACA	Increase infliximab	1/6 (17)	$P < 0.004$
	Change anti-TNF	11/12 (92)	
Subtherapeutic concentration	Increase infliximab	25/29 (86)	$P < 0.016$
	Change anti-TNF	2/6 (33)	

HACA, human anti-chimeric antibody; TNF, tumor necrosis factor.