GASTROENTEROLOGY & HEPATOLOGY
The Independent Peer-Reviewed Journal

July 2014 Volume 10, Issue 7, Supplement 4

A SPECIAL MEETING REVIEW EDITION

Highlights in Anti-Tumor Necrosis Factor Monitoring and Antibody Monitoring From the 2014 DDW Meeting

Digestive Disease Week 2014

May 3-6, 2014 • Chicago, Illinois

Special Reporting on:

- Therapeutic Monitoring of Anti-TNF Levels and Antibodies to Predict Response and Achieve Mucosal Healing
- Prospective Therapeutic Drug Monitoring and Optimization of Infliximab Maintenance Therapy in IBD
- Classification of Non-IBD, Crohn's Disease and Ulcerative Colitis in a Young Patient Population Using a Multi-Marker Diagnostic Panel
- Persistence of Antibodies to Infliximab for More Than Two Months Predicts Loss of Response to Infliximab in Inflammatory Bowel Diseases
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- ATG16L1 Genotype Is Associated With Response to Anti-TNF

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Supported through funding from Prometheus Laboratories Inc.

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Therapeutic Monitoring of Anti-TNF Levels and Antibodies to Predict Response and Achieve Mucosal Healing

Paul J. Rutgeerts

In an oral presentation at Digestive Disease Week 2014, Paul J. Rutgeerts, MD, PhD, presented an overview of therapeutic drug monitoring in patients with inflammatory bowel disease (IBD).[1] Treatment of IBD, including ulcerative colitis (UC) and Crohn's disease (CD), has been revolutionized by the introduction of therapeutic antibodies against tumor necrosis factor-α (TNFα), a key proinflammatory cytokine. By neutralizing TNFα activity, antibodies such as infliximab and adalimumab promote mucosal healing and induce long-term remissions in many patients.[2] However, some patients fail to respond to anti-TNFα antibody therapy. In patients with a true primary nonresponse, drug levels are in the therapeutic range, but the response is poor, likely indicating a disease mechanism that does not involve TNFα as the primary inflammatory pathway. In contrast, secondary nonresponse occurs when a patient who initially responded to the anti-TNFα agent subsequently loses response, which may indicate the presence of anti-drug antibodies. For both situations, therapeutic drug monitoring provides an essential tool for evaluating subsequent treatment options.

Higher Serum Infliximab Levels Are Associated With Improved Outcomes

ACT1 and ACT2 (Active Ulcerative Colitis Trials 1 and 2) examined the efficacy of infliximab induction and maintenance therapy in patients with moderate-to-severe, active UC despite treatment.[3] Each trial enrolled 364 adults to receive placebo or infliximab (5 mg/kg or 10 mg/kg) intravenously at weeks 0, 2, and 6, then every 8 weeks through week 46 (ACT1) or week 22 (ACT2). Patients were followed for 54 weeks in ACT 1 and for 30 weeks in ACT 2. Both trials showed a significant benefit for infliximab over placebo, with infliximab resulting in a greater likelihood of clinical response at weeks 8, 30, and 54. A sub-analysis of patients who received the lower infliximab dose examined the relationship between serum concentration of infliximab and patient outcomes.[4] Despite the fact that all patients had received the same dose of infliximab, the serum drug concentration ranged from less than 21.3 µg/mL in the lowest quartile to greater than 47.9 µg/mL in the highest quartile at 8 weeks. The proportion of patients achieving clinical remission, as assessed by the Mayo Score, increased with increasing quartiles of serum infliximab concentration at weeks 8 (P=.0504), 30 (P<.0001), and 54 (P=.0066). A direct correlation with serum infliximab concentration was also observed for clinical response and mucosal healing.

A similar relationship was observed in an open-label, multicenter, phase 3 study of pediatric patients with moderate-to-severe UC.[5] Sixty patients aged 6 to 17 years received induction infliximab (5 mg/kg) at weeks 0, 2, and 6. The 45 responders at week 8 were randomized to receive the same dose of infliximab every 8 weeks through week 46 or every 12 weeks through week 42. Doses were increased or the interval between infusions was decreased for patients who lost response during the maintenance phase. At week 8, patients with serum infliximab concentrations of at least 41.4 µg/mL had higher rates of clinical response, mucosal healing, and clinical remission (92.9%, 92.9%, and 64.3%, respectively) compared with patients who had serum infliximab concentrations lower than 18.1 µg/mL (53.9%, 53.9%, and 30.8%, respectively). The results are in keeping with early observations that showed a positive association between higher trough levels of serum infliximab during maintenance and decreased levels of C-reactive protein (CRP) and higher rates of endoscopic improvement in CD patients.[6]

Optimizing Trough Levels of Infliximab and Adalimumab

Drug monitoring in order to individualize dosing may prove most beneficial in patients who initially show a poor or absent response. In addition, individualized dose adjustments may be appropriate as the inflammatory burden changes. Because the relationship between drug dose and drug exposure varies from patient to patient, more frequent monitoring of serum drug levels and appropriate dose adjustments may be necessary to maintain effective drug concentrations. To determine the effective drug concentration in patients with CD, a study examined the relationship between serum infliximab levels, antibodies to infliximab (ATI), and CRP levels in samples from 532 patients.[7] Serum samples were from patients in 4 prospective randomized clinical trials or cohort studies that evaluated the maintenance phase of infliximab treatment. Serum infliximab and ATI levels were measured using a mobility-shift assay based on high-performance liquid chromatography.[8] CRP levels were assessed by the enzyme-linked immu-

nosorbent assay (ELISA) and served as a measure of disease activity. The study examined the relationship between pairs of serum samples showing infliximab and ATI levels at an initial time point and CRP level in a sample from a subsequent time point. In patients with ATI, serum drug levels appeared to have little impact on disease activity. However, in patients without ATI, infliximab levels below 3 µg/mL were associated with increased disease activity compared with patients exhibiting a higher drug concentration, as reflected in a higher level of CRP (P<.001), thus suggesting that maintaining a serum infliximab concentration of at least 3 µg/mL could improve response rates in patients without antidrug antibodies.

The concept of exposure-response relationships has also been demonstrated for adalimumab. In an observational study, patients with CD who had failed infliximab were treated with adalimumab. Of the 156 patients who received maintenance therapy, 60 patients (38.5%) eventually discontinued due to a loss of response, and serum trough levels of adalimumab were lower in patients who discontinued.[9] Extending the concept of exposure-response, a small cross-sectional study investigated the association between adalimumab trough levels and mucosal healing.[10] The study enrolled 40 patients with CD or UC who received adalimumab maintenance therapy and whose disease activity was evaluated by endoscopy. Trough drug levels and antibodies to adalimumab (ATA) were also measured. Patients with clinical remission showed a higher trough level of adalimumab vs patients with active disease (6.02 µg/mL vs 3.2 µg/mL; P=.012). A higher level of drug was also observed in patients with mucosal healing vs those without (6.5 µg/mL vs 4.2 µg/mL; P<.005). Absence of mucosal healing was associated with trough levels below 4.9 µg/mL.

A post-hoc analysis of data from the multicenter, placebo-controlled ACCENT 1 (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen I) study demonstrated a relationship between serum trough levels of infliximab and long-term response.[11] After 14 weeks of induction therapy, serum infliximab trough levels and CRP were measured. Infliximab levels and CRP levels, relative to baseline, at week 14 were compared in patients with or without a durable response at week 54. In patients with vs without a durable response, median trough infliximab levels were 4.0 µg/mL vs 1.9 µg/mL, respectively (P=.0331). Serum infliximab trough levels of at least 3.5 µg/mL, as well as a decrease in CRP of at least 60% from baseline, both measured at week 14, were associated with achieving a sustained response (ORs, 3.5 [95% CI, 1.1-11.4] and 7.3 [95% CI, 1.4-36.7]).

Optimizing Trough Levels in the TAXIT Trial

The TAXIT (Trough Level Adapted Infliximab Treatment) study was performed to test the idea that achieving serum trough levels of infliximab between 3 µg/mL and 7 µg/mL would lead to improved outcomes in patients with IBD.[12] The patients in this study were all on maintenance infliximab. In the initial, optimization phase of the study, patient drug levels were optimized to a value between 3 µg/mL and 7 µg/mL. After the desired drug levels were reached, patients were then randomized to receive infliximab dosing based on 1 of 2 measures: clinical factors, including disease symptoms and CRP levels; or serum drug level, which was maintained within the proposed optimal levels. The primary endpoint was the rate of clinical and biological remission 1 year after randomization. Baseline drug levels, assessed prior to the dose optimization phase, showed that only 44% of patients had a serum infliximab concentration within the range of 3 µg/mL to 7 µg/mL. At trough, drug was undetectable in 9% of patients, and thus it is likely that these patients were not benefitting from the medication Twenty-one percent of patients had infliximab levels below 3 µg/mL and required a dose increase, whereas the remaining 26% of patients had serum drug levels above 7 µg/mL, resulting in a dose decrease. Improved disease control was observed in patients who initially demonstrated suboptimal serum drug levels and were treated with a dose increase. In addition, dose adjustment increased the proportion of patients in complete remission among patients with CD, but not UC. For patients with initially high drug levels, the dose decrease did not diminish disease control, based on clinical remission and CRP levels, but treatment costs were reduced. However, for the randomized maintenance phase, the primary endpoint analysis showed no significant differences in monitoring by drug and anti-drug antibody level as compared with monitoring by clinical judgment. Thus, this study suggests that clinical monitoring may be adequate after an initial laboratory-based optimization of serum infliximab levels.

Antibodies to Infliximab and the Use of Immunosuppressants

As demonstrated in SONIC (Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease), the combination of infliximab plus azathioprine improved the rate of corticosteroid-free clinical remission compared with either infliximab or the immunosuppressant alone.[13] The randomized, double-blind, phase 3b study evaluated the efficacy of infliximab monotherapy, azathioprine monotherapy, or concomitant use of these agents in 508 adults with moderate-to-severe Crohn's disease without prior exposure to immunosuppressive or biologic therapies. Patients were randomized evenly to

receive 30 weeks of treatment consisting of either infliximab (5 mg/kg) at weeks 0, 2, and 6, then every 8 weeks; azathioprine (2.5 mg/kg) daily; or the 2 drugs in combination. Compared with infliximab monotherapy, the combined therapy not only improved the remission rate but also reduced the incidence of ATI and increased infliximab trough levels. At week 30, ATI were observed in 1 of 116 patients (0.9%) receiving combination therapy vs 15 of 103 patients (14.6%) receiving infliximab monotherapy. Also at week 30, median trough levels of infliximab were 3.5 µg/mL for patients receiving 2-drug therapy vs 1.6 µg/mL for infliximab alone, further underscoring the relationship between optimal drug levels and patient responses in light of the improved response rate for the combination treatment.

Although the presence of ATI can lead to a permanent loss of response, some patients experience a transient antibody response. A retrospective study examined 1232 serum samples from 64 CD patients and 26 UC patients. Testing the serum samples with the homogenous mobility shift assay (HMSA) revealed ATI in 53 of 90 patients (59%). In 15 of the 53 patients (28%), ATI disappeared over time, and only 2 (13%) of these patients discontinued infliximab therapy. In contrast, 26 of 38 patients (68%) with sustained ATI discontinued treatment.[14] Although many patients with sustained ATI experience a complete loss of response, treatment with an immunosuppressant may overcome ATI. In a retrospective analysis of 5 patients who had developed ATI, 3 patients received azathioprine or 6-mercaptopurine and 2 patients received methotrexate. All patients showed decreasing levels of ATI and increasing trough levels of infliximab. Competition assays demonstrated increased drug activity in serum in parallel with the reduction of ATI.[15]

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Prospective Therapeutic Drug Monitoring and Optimization of Infliximab Maintenance Therapy in IBD

Byron P. Vaughn, Manuel Martínez-Vazquez, Vilas Patwardhan, Alan C. Moss, William J. Sandborn, and Adam S. Cheifetz

Although infliximab is an effective treatment for IBD, responses may diminish over time. The development of ATI may cause secondary loss of response and concomitant resurgence of symptoms and antibody-mediated side effects. Several studies have now bolstered the concept that establishing a minimum infliximab trough concentration leads to improved outcomes in patients with IBD. In an early study in CD patients, detectable infliximab levels were associated with reduced CRP levels as well as improved rates of clinical and endoscopic remission.[1] More recent studies suggest that an optimal trough infliximab concentration ranges from approximately 3 µg/mL to 5 µg/mL and is associated with greater rates of sustained response and reduced CRP levels.[2-6] The idea of monitoring drug concentration to improve patient outcomes has been further underscored in patients with UC. In a retrospective study of 135 consecutive UC patients who received induction and maintenance infliximab therapy, low trough levels soon after induction were associated with a higher risk of loss of response and discontinuation, and a minimum trough level of 7.19 µg/mL was associated with a sustained response.[5]

Despite the growing data to support the benefits of optimizing serum infliximab levels, testing for drug levels continues to be performed largely as a reactive measure in patients showing a loss of response to infliximab. In an oral presentation at Digestive Disease Week 2014, Vaughn and colleagues presented results from a study showing that prospectively optimizing infliximab drug levels improves patient outcomes and reduces discontinuations.[7] Starting in 2009, one of the study authors (Dr Cheifetz) began prospectively monitoring infliximab trough concentrations with the goal of maintaining detectable trough levels (in 2010, the target trough level was increased to a range of 5 µg/mL to 10 µg/mL). All patients included in the analysis underwent drug level testing with the proactive goal of optimizing the dose; patients who underwent testing in response to increased IBD symptoms or side effects were excluded. Patients who were on infliximab and in clinical remission but did not undergo infliximab dose optimization were used as the control group. Patient charts were reviewed for demographics, duration of infliximab therapy, and reasons for discontinuation. Starting in 2009, 48 patients who underwent dose optimization were identified, and 78 patients qualified for the control group. Demographics were similar between the 2 groups. Patients had a median age of 35 years (range, 26.2-49.7 years). More than two-thirds of patients had CD, approximately one-

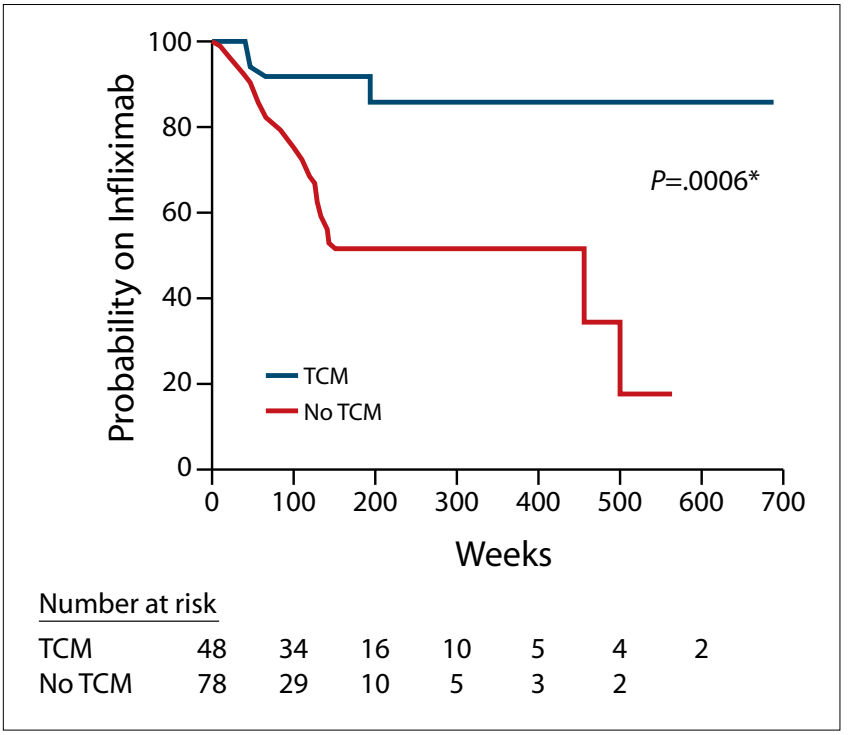

Figure 1. Duration of infliximab therapy. TCM, trough concentration monitoring. Adapted from Vaughn BP et al. DDW abstract 209. *Gastroenterology*. 2014;146(suppl 1):S54.[7]

fourth had UC, and the remainder had unclassified IBD. In both groups, 19% of patients had undergone prior IBD surgery. Initially, 24% of patients in the drug optimization group had undetectable drug trough concentrations, and the infliximab dose was escalated in 44%. Discontinuations were significantly less frequent in the drug level optimization group compared with the control group (10% vs 31%; *P*=.009), and patients in the optimization group were significantly more likely to continue infliximab therapy for a longer duration (*P*=.0006; Figure 1). Fifteen patients in the control group and 0 patients in the optimization group discontinued due to ongoing IBD symptoms. Patients in the optimization group who achieved a trough concentration of at least 5 µg/mL received infliximab for a longer duration compared with patients who had a lower concentration (*P*=.0001).

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Classification of Non-IBD, Crohn's Disease and Ulcerative Colitis in a Young Patient Population Using a Multi-Marker Diagnostic Panel

Steven Lockton, Fred Princen, and Sharat Singh

Patients younger than 18 years account for up to 15% of IBD cases.[1] The disease is generally diagnosed with a combination of clinical examination, imaging, endoscopy with histopathology, and laboratory testing. The development of less invasive modalities is desirable, particularly for younger patients, so that testing with serological markers could provide an attractive option. A recent analysis investigated the value of assessing combinations of markers for the diagnosis of IBD and differentiation of CD and UC in adults.[2] In addition to evaluating autoantibodies and antimicrobial antibodies, the analysis included markers of inflammation and genetic variants involved in processes such as innate immunity, adaptive immunity, and barrier functions. Although many serum biomarkers of IBD have been evaluated in adults, their value in diagnosing pediatric disease has been less well studied.

Table 1. Results of Biomarker Testing in Young IBD Patients

%	IBD	CD	UC
Sensitivity	86.1	91.9	82.1
Specificity	86.0	75.8	90.5
PPV	95.4	92.7	67.6
NPV	64.5	73.5	95.5
Accuracy	86.1	88.2	88.9

CD, Crohn's disease; IBD, inflammatory bowel disease; NPV, negative predictive value; PPV, positive predictive value; UC, ulcerative colitis.

Data from Lockton S et al. DDW abstract 999. *Gastroenterology*. 2014;146(suppl 1).[3]

In a poster presented at Digestive Disease Week 2014, Steven Lockton, PhD, presented results of a study evaluating a biomarker test to identify and stratify young IBD patients.[3] Samples from 251 patients with a median age of 15 years (interquartile range, 13-16 years) were collected from 15 North American gastrointestinal centers. One hundred forty-seven patients had CD (59%), 47 had UC (19%), and 57 samples represented non-IBD controls (23%). The evaluation queried antineutrophil cytoplasmic antibodies (ANCA) and perinuclear ANCA (pANCA), as well as antibodies to *Saccharomyces cerevisiae* (ASCA IgA and IgG), outer membrane protein C (anti-OmpC), and flagellin (anti-Fla2, anti-FlaX, and anti-CBir1). The test also queried 4 gene variants (ATG16L1, NKX2-3, ECM1, and

STAT3) and 5 markers of inflammation (CRP, serum amyloid A, intercellular adhesion molecule, vascular cell adhesion molecule, and vascular endothelial growth factor). Many of these markers may be useful not only for distinguishing IBD from healthy patients, but also for differentiating CD from UC. A machine-learning model was used to identify markers associated with IBD, CD, and UC. The diagnostic model had a sensitivity of 86.1% and a specificity of 86.0% for identifying pediatric patients with IBD (Table 1). Among patients classified as IBD, the model identified CD patients with a sensitivity of 91.9% and a specificity of 75.8%, and it identified UC patients with a sensitivity of 82.1% and a specificity of 90.5%. The diagnostic accuracy of the model was 86.1% for IBD compared with non-IBD, 88.2% for CD, and 88.9% for UC. The negative and positive predictive values of the biomarkers were 64.5% and 95.4% for IBD, 73.5% and 92.7% for CD, and 95.5% and 67.6% for UC, all respectively.

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Persistence of Antibodies to Infliximab for More Than Two Months Predicts Loss of Response to Infliximab in Inflammatory Bowel Diseases

Manon Leclerc, Hubert Marotte, Stephane Paul, Emilie Del Tedesco, Jean Marc Phelip, Laurent Peyrin-Biroulet, and Xavier Roblin

Patients with IBD who are treated with infliximab may develop ATI, largely due to the presence of murine antibody sequences in the F(ab)2 region of the therapeutic agent. ATI may reduce the efficacy of infliximab, as shown in a recent meta-analysis that reported a 3-fold increase in the risk of loss of response in CD patients with ATI compared with patients lacking ATI (P<.0001).[1] A retrospective study of 90 patients demonstrated that persistently high levels of ATI lead to a permanent loss of response; however, ATI are transient in some patients and do not always lead to a worse clinical outcome.[2] In a poster presented at Digestive Disease Week 2014, Manon Leclerc, MD, and colleagues provided results from a prospective study investigating the ability of ATI to predict loss of response in patients with IBD.[3] Loss of clinical response was defined as an increase in clinical symptoms requiring a therapeutic adjustment, such as infliximab dose intensification, initiation of another medication, or surgery.[4] CRP was followed as a marker of disease activity.[4] The study included 481 blood samples from 93 consecutive IBD patients, including 59 with CD, who were treated with infliximab. Patients had a mean age of 30 years, and the mean duration of follow-up was 17.2 months. Loss of clinical response was demonstrated in 32 patients (34.4%). Thirty-four patients (38%) had normal CRP, and 27 patients (29%) had detectable ATI. Of the patients with ATI, 14 (51.9%)

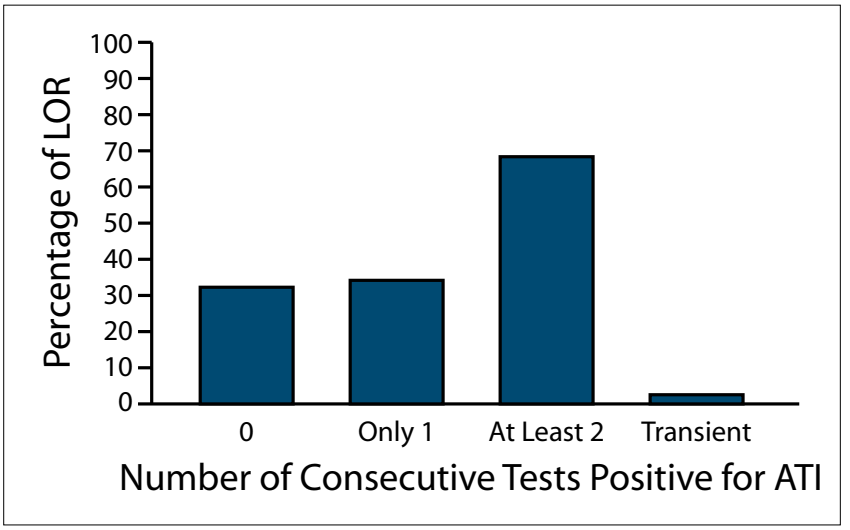

Figure 2. Correlation between loss of response and consecutive positive measurement of antibodies to infliximab. LOR, loss of response. Adapted from Leclerc M et al. DDW abstract Sa1257. *Gastroenterology*. 2014;146(suppl 1):S245.[3]

had only 1 ATI-positive sample; in 13 patients (48.1%), more than 50% of the samples were ATI-positive.

The presence of ATI was significantly associated with loss of response (*P*=.011) and positive CRP (*P*=.0003). An ATI threshold of greater than 20 ng/mL in the first sample predicted loss of response with 94% specificity and 22% sensitivity (likelihood ratio, 3.39; area under receiver operating characteristic curve, 0.59). An increasing number of consecutive samples positive for ATI correlated to an increasing likelihood of loss of response. Presence of positive ATI in more than 50% of a patient's samples was associated with more than 50% loss of response to IFX during follow-up, and with systematic clinical relapse in the case of permanent ATI (*P*=.0044). However, transient ATI (present in only 1 sample) were not associated with loss of response (*P*=.01; Figure 2). Other factors not associated with loss of response included concomitant thiopurines, and infliximab duration and dose. Based on univariate analysis, predictive factors of loss of response included an ATI level greater than 20 ng/mL (*P*=.0071), CRP levels greater than 5 mg/L (*P*=.0046), and clinical activity (*P*=.0026). By multivariate analysis, the individual factors of ATI level greater than 20 ng/mL and CRP level greater than 5 mg/L were associated with relative risks of maintaining clinical remission of 0.64 (95% CI, 0.46-0.90) and 0.65 (95% CI, 0.43-0.90), respectively, and, these 2 factors combined produced an increased relative risk of 0.21 (95% CI, 0.08-0.55).

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Pre-Operative Serological Markers May Predict Postoperative Crohn's Disease Recurrence: Results From a Prospective Mono-Centric Trial

Marc Ferrante, Manuel Noben, Anthony de Buck van Overstraeten, Steven Lockton, Gert De Hertogh, Fred Princen, Albert M. Wolthuis, Gert A. Van Assche, Severine Vermeire, Sharat Singh, and Andre D'Hoore

Postoperative clinical and endoscopic recurrence of CD is a common and challenging problem in patients who undergo intestinal resection. Ten years after surgery, half of patients will experience recurrence of symptoms, with 35% requiring additional surgery.[1] Postoperative prophylactic therapy with various drugs has produced mixed results, and treatment risks must be weighed against potential benefits. Selecting patients with specific risk factors may help guide treatment to those who are most likely to benefit. Risk factors for recurrence that have been identified to date include previous resections, fistulizing disease, active smoking, and myenteric plexitis.[2] Serological markers have been associated with more aggressive CD. They may provide further insights regarding patient risk for recurrence and have yet to be fully elucidated in this context.[3]

In a poster presented at Digestive Disease Week 2014, Mark Ferrante, MD, and colleagues described results from a study evaluating the use of preoperative serological markers to predict postoperative clinical and endoscopic recurrence.[4] The study enrolled 100 consecutive patients with a median age of 41.7 years and included 41 men and 27 active smokers. All patients were undergoing ileal resection with ileocolonic anastomosis for refractory CD. A serum sample was collected from each patient within 1 week before surgery. All patients were followed prospectively with postoperative endoscopic evaluation at 6 months. The primary endpoint was endoscopic recurrence, defined as a postoperative endoscopic recurrence Rutgeerts score of i3 (denoting diffuse aphthous ileitis with diffusely inflamed mucosa) or i4 (marked by diffuse inflammation with larger ulcers, nodules and/or narrowing).[5] Clinical relapse was defined as recurrence of CD symptoms during follow-up, with CD activity confirmed by serology, endoscopy, or radiology. Time to clinical recurrence was a secondary endpoint. Blinded sera were analyzed by ELISA at an indepen-

Table 2. Predictors of Recurrence: Univariate Analysis

	Endoscopic Recurrence	Clinical Recurrence		
	Odds Ratio	**95% CI**	***P* Value**	***P* Value**
ASCA IgA >90 EU	0.93	0.32-2.67	.894	.969
ASCA IgG >94 EU	0.09	0.01-0.69	.004	.073
CBir1 >80 EU	1.23	0.44-3.42	.689	.968
Fla2 >66 EU	3.42	1.28-9.12	.011	.021
FlaX >92 EU	3.42	1.28-9.12	.011	.063
OmpC >13 EU	1.61	0.59-4.36	.351	.407
pANCA positive	3.27	1.16-9.24	.021	.008
CRP >5 mg/L	2.64	0.99-7.06	.049	.761
Active smoking	2.90	1.11-7.60	.027	.019

ASCA, anti-*Saccharomyces cerevisiae* antibodies; CRP, C-reactive protein; Ig, immunoglobulin.

Data from Ferrante M et al. DDW abstract Su1349. *Gastroenterology*. 2014;146(suppl 1).[4]

dent laboratory for the expression of anti-*Saccharomyces cerevisiae* antibodies (ASCA) immunoglobulin A and immunoglobulin G and the atypical antibody pANCA, and for antibodies against 3 flagellar markers (Fla2, FlaX, and CBir1) and the bacterial protein OmpC. The cutoff point was defined as the value for the third quartile of each individual marker as determined in this population. A cumulative risk score was developed by combining all independent risk factors.

Thirty-four patients had received prior resection, 26 had familial IBD, and 27 patients were active smokers. Baseline CRP was greater than 5 mg/L in 55 patients. Endoscopic recurrence was observed in 25 patients, and clinical relapse within 24 months of follow-up was observed in 29 patients. Based on multivariate analysis, factors independently associated with endoscopic recurrence included an anti-Fla2 antibody level greater than 66 ELISA units (EU; odds ratio, 3.0 [95% CI, 1.1-8.7]; *P*=.037) and active smoking (odds ratio, 3.1 [95% CI, 1.1-8.8]; *P*=.029). Factors independently associated with clinical recurrence included anti-Fla2 antibody level greater than 66 EU (odds ratio, 2.2 [95% CI, 1.0-4.6]; *P*=.041), pANCA positivity (odds ratio, 2.5 [95% CI, 1.2-5.4]; *P*=.016), and active smoking (odds ratio, 2.6 [95% CI, 1.2-5.5]; *P*=.011; Table 2). A cumulative risk score was developed by combining the 3 risk factors associated with endoscopic or clinical recurrence. This cumulative risk score successfully predicted the likelihood of both endoscopic relapse (*P*<.001) and clinical relapse (*P*<.001), and yielded a gradual increase in relapse rate as a function of an increasing number of risk factors.

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Antibodies and Levels of Biologics—Reactive vs Proactive Measurements

Adam S. Cheifetz

In an oral presentation at Digestive Disease Week 2014, Adam S. Cheifetz, MD, discussed several clinical trials evaluating therapeutic drug monitoring of anti-TNFα antibodies and suggested that proactive therapeutic drug monitoring to achieve serum drug concentrations within a desired range may improve responses in patients with IBD.[1] CD and UC affect approximately 1.4 million Americans, with nearly 30,000 new cases identified each year.[2] Despite novel treatments, relapse is common, with most patients experiencing some form of chronic disease. Surgery is often indicated for patients who fail to respond to treatment or develop complications. A 2007 study showed that surgery rates for CD patients had remained stable during the prior decade, whereas hospitalization rates had increased significantly since 1990.[3]

IBD patients being treated with infliximab who develop active disease present a common treatment conundrum. Possible next treatment steps include increasing the infliximab dose or decreasing the interval of infliximab infusion based on clinical evaluation alone or the level of infliximab and ATI. ATI could be assessed to determine the patient's actual exposure to the drug. A retrospective analysis of 155 patients

showed that testing for serum infliximab and ATI levels impacted treatment decision-making for approximately three-fourths of patients with IBD symptoms.[4] The majority of patients were tested due to loss of response to infliximab (49%) or partial response after initiating infliximab (22%). Of the ATI-positive patients, a complete or partial response was achieved by 92% of those who changed to a different anti-TNFα and only 17% of patients who had dose escalation. Among patients with subtherapeutic concentrations of infliximab, 86% experienced a complete or partial clinical response following dose escalation, whereas switching to a different anti-TNFα agent yielded a response in only one-third of patients. This modest response from switching to a different anti-TNFα agent is similar to results from the GAIN (Gauging Adalimumab Efficacy in Infliximab Non-Responders) study, in which 325 CD patients with active disease who had either lost response or become intolerant to infliximab were randomized to receive adalimumab induction therapy or placebo.[5] Adalimumab (160 mg at week 0, then 80 mg at week 2) induced remissions at week 4 in 21% of patients vs 7% of patients receiving placebo (P<.001). The majority of patients failed to respond to the new drug, suggesting that at least some of these patients may have clinical symptoms in the absence of active inflammation. For these patients, escalating the dose of anti-TNFα or switching to a similar drug exposes the patient to a greater level of biologic therapy, thus increasing the risks with no added benefit. In contrast, patients who had developed antibodies to the infliximab may benefit from switching to adalimumab, as previously shown.[4]

Determining the correct therapeutic dose for any drug requires a balance between achieving efficacy while limiting toxicity. With therapeutic antibodies, subtherapeutic drug levels may prime the immune system to develop antidrug antibodies. Studies examining the optimal therapeutic level of infliximab for patients with CD suggest a dose of at least 3 µg/mL and possibly greater than 5.5 µg/mL, as these levels are associated with higher rates of clinical remission, sustained responses, and reduced CRP levels.[6-8] Undetectable levels of drug are consistently associated with loss of response. The concept of minimal effective therapeutic concentrations also applies to patients with UC, although an infliximab level of at least 7 µg/mL may be optimal for these patients.[9,10] Similarly, an adalimumab level greater than 5 µg/mL predicted normal CRP and remission and was associated with a decrease in drug discontinuation in patients with IBD.[11] For certolizumab pegol, higher concentrations of the drug detected at week 8 after initiating therapy were associated with endoscopic response (P=.0016) and remission (P=.0302) at week 10 in CD patients with moderate-to-severe ileocolonic disease.[12]

Proactive Optimization of Drug Trough Levels

In the TAXIT study, 178 patients with CD and 85 patients with UC, all in remission on maintenance therapy, were first dose-optimized to a serum concentration level between 3 µg/mL and 7 µg/mL.[8] After the adjustment of drug levels, patients were randomized to infliximab dosing based on clinical symptoms and CRP levels or to dosing based on serum infliximab concentration. Patients with elevated ATI and no detectable trough infliximab were not included in the randomization, whereas patients with lower levels of ATI and detectable trough infliximab were dose-adjusted and included. The primary outcome was clinical remission at 1 year. The initial testing results from the optimization phase showed that nearly one-third of patients had levels of serum infliximab of less than 3 µg/mL, including 9% of patients with undetectable levels. Approximately one-fourth had serum infliximab levels exceeding the therapeutic dose limit of greater than 7 µg/mL. Observations at 1 year after the randomization showed no difference in remission rates between dosing based on clinical factors vs dosing based on serum infliximab concentrations. However, the clinically based dosing group had an increased need for rescue therapy compared with patients whose dosing was based on trough levels.

Dr Cheifetz reviewed findings that he co-authored, and were described in a presentation by Vaughn and colleagues, in which patients' infliximab doses were adjusted to achieve a serum concentration between 5 µg/mL and 10 µg/mL based on drug monitoring.[13] The primary outcome was duration of infliximab therapy based on a time-to-event curve, with patients censored at the time of their final chart review. Secondary outcomes included infliximab discontinuation, trough concentrations, and dosing changes. The retrospective evaluation of patient charts yielded 48 patients who had been proactively tested and dose adjusted and 78 patients who were conventionally managed. As with the TAXIT trial, a large percentage of patients initially had infliximab levels outside the target range. The group of patients who received proactive monitoring had a significantly longer duration of infliximab therapy than the conventionally managed group (P=.0006). After 1 year, patients in both groups appeared to have a similar probability of remaining on infliximab. However, after 2 or more years, the patients who achieved trough levels of at least 5 µg/mL had a much greater likelihood of continuing to receive infliximab compared with patients whose levels were lower (P<.001) as well as patients whose levels were not tested (P<.001). Approximately 3 times as many conventionally managed patients discontinued infliximab over the study period, including 15 patients who stopped due to IBD symptoms and 6 patients who had

acute infusion reactions. Dr Cheifetz noted several study limitations, including its retrospective nature, the fact that all patients were treated at a single center, and the potential for confounding between the 2 groups.

Combination Therapy

A recurring theme in the treatment of IBD involves the relative risks and benefits of combination therapy vs monotherapy. Early studies suggested that the addition of immunomodulators to anti-TNFα agents did not improve outcomes. However, immunomodulators have consistently been associated with increased trough levels and decreased rates of ATI. Both the SONIC and SUCCESS (Infliximab, Azathioprine, or Infliximab + Azathioprine for Treatment of Moderate to Severe Ulcerative Colitis) trials demonstrated improved outcomes with combination therapy vs monotherapy. SONIC showed a 56.8% corticosteroid-free remission rate at week 26 for CD patients receiving combination therapy vs 44.4% for patients receiving infliximab monotherapy (P=.02) and 30.0% for patients receiving azathioprine monotherapy (P<.001).[14] Mucosal healing rates were also superior for combination therapy vs infliximab (P=.06) or azathioprine (P<.001). The randomized, double-blind SUCCESS trial evaluated similar treatment strategies in patients with moderate to severe UC.[15] Patients were randomized to receive infliximab (5 mg/kg at weeks 0, 2, 6, and 14) by intravenous infusion plus daily oral placebo capsules; oral azathioprine (2.5 mg/kg daily) plus placebo infusions; or combined therapy. The primary endpoint was corticosteroid-free remission at week 16. The primary endpoint was achieved by 31 of 78 patients (39.7%) receiving the combination therapy vs 17 of 77 (22.1%) patients receiving infliximab monotherapy (P=.017) and 18 of 76 patients (23.7%) receiving azathioprine monotherapy (P=.032). Mucosal healing at week 16 was significantly increased in patients receiving combination therapy compared with those receiving azathioprine alone (62.8% vs 36.8%; P=.001), although it was not increased compared with patients receiving infliximab alone (62.8% vs 54.6%; P=.295). Combination therapy may succeed by helping patients maintain a therapeutically effective concentration of drug, perhaps by reducing the development of antidrug antibodies.

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Higher 6-Thioguanine Nucleotide Concentrations Are Associated With Higher Trough Levels of Infliximab in Patients on Combination Therapy

Andres Yarur, Maddie Kubiliun, Katherine Drake, Scott Hauenstein, Jamie S. Barkin, Daniel A. Sussman, Amar R. Deshpande, Maria A. Quintero, Sharat Singh, and Maria T. Abreu

Thiopurines are often used in combination with other agents, such as infliximab, in the treatment of IBD. Higher levels of the thiopurine metabolite 6-thioguanine have been linked to improved outcome.[1] A study by Andres Yarur, MD, and coworkers aimed to determine whether levels of 6-thioguanine and infliximab and ATI were correlated.[2] The study included 72 IBD patients who had been receiving maintenance therapy with IFX in combination with a thiopurine (azathioprine or 6-mercaptopurine) for at least 4 months.

Levels of 6-thioguanine were positively associated with IFX levels (rho: 0.477 [*P*<.0001]). The IFX level was not associated with the thiopurine dose (rho: -0.05 [*P*=.71] or the lymphocyte count (rho, 0.12 [*P*=0.3]). The best predictor of higher anti-TNF levels was a 6-thioguanine level greater than or equal to 125 pmol/8 × 10^8 red blood cells (ROC: 0.82; *P*=.002). Levels of 6-thioguanine and 6-methylmercaptopurine were positively associated (rho: 0.42; *P*<.001), but a multiple regression analysis showed that only the 6-thioguanine level was predictive of IFX measurement (*P*<.001). There was a negative association between higher 6-thioguanine levels and the lymphocyte count (rho: -0.36; *P*=.002). ATI were detected in 8 patients (11%); these patients were more likely to have lower levels of 6-thioguanine (Table 3). The authors concluded that lower target 6-thioguanine levels (125 pmol/8 × 10^8 red blood cells) could maximize infliximab levels while minimizing toxicity in IBD patients who are receiving combination therapy.

Table 3. Comparison of Patients With and Without Detectable ATI

	With ATI	Without ATI	*P* Value
Female sex, n (%)	7 (87.5)	34 (53.1)	.06
Age, mean years (SD)	41 (12)	36 (14)	.26
Thiopurine dose, mean mg (SD)	112 (44)	142 (60)	.12
Lymphocyte count, mean cell × 10^3/mL (SD)	1.7 (0.8)	1.8 (0.7)	.81
White blood cells, mean cell × 10^3/mL (SD)	7.1 (1.7)	6.8 (2.2)	.66
6-Thioguanine, pmol/8 × 10^8 red blood cells (SD)	116.7 (75)	193 (88)	.024
6-Methylmercaptopurine, pmol/8 × 10^8 RBC (SD)	1,419 (3,135)	3,661 (4,942)	.1

ATI, antibodies to infliximab; SD, standard deviation.

Data from Yarur A et al. DDW abstract. *Gastroenterology*. 2014;146(suppl 1):S245.[2]

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The Clinical and Immunological Significance of Low Levels of Infliximab in the Absence of Anti-Infliximab Antibodies in Patients With IBD

Bella Ungar, Adi Anafy, Uri Kopylov, Yulia Ron, Henit Yanai, Iris Dotan, Yehuda Chowers, Abraham R. Eliakim, and Shomron Ben-Horin

Although ATI may lead to low serum trough levels of infliximab, some IBD patients with low or undetectable drug trough levels also appear to not have ATI. The mechanism for such "double-negative" patients is unclear and could arise from technical assay limitations, such that ATI are present but not detected. In a poster presented at Digestive Disease Week 2014, Bella Ungar and colleagues described results from a study investigating outcomes in double-negative patients as well as ATI and serum infliximab status using 2 different types of ELISA.[1] The double-antigen ELISA is commonly used to detect ATI but, because infliximab is used as both the capture antigen and the labeled detection antibody, serum infliximab interferes with measurement of ATI. An alternative method uses a conjugated detection antibody that recognizes the human λ chain, thus circumventing binding to the κ chains that are present on infliximab.[2] Serum samples from IBD patients treated with infliximab were collected prospectively between 2009 and 2013. Samples of patients with loss of response were tested for ATI and infliximab trough levels using both the double-antigen ELISA and an alternate, λ-chain method. To increase the likelihood of detecting low levels of ATI or infliximab, 46 double-negative patients were randomly selected for further testing at a 1:10 serum dilution. To evaluate the relationship between double-negative status and clinical outcome, 30 double-negative patients were matched with 30 IFX-positive, ATI-negative controls, and ATI levels as well as clinical outcomes were determined.

The double-antigen ELISA yielded a double-negative rate of 35.5% (27 out of 76 samples tested), whereas the λ-chain ELISA yielded a double-negative rate of 13% (25 of 188 samples tested) in patients with loss of response (P<.001). The majority of samples deemed double-negative (n=27) by the double-antigen ELISA were found to be either infliximab-positive (44%), ATI-positive (30%), or double-positive (3%) by the λ-chain ELISA. Moreover, with λ-chain ELISA testing of the 46 serum samples diluted 1:10, only 1 sample (2%) was double-negative. Prospective follow-up of patients with double-negative serum samples showed a higher rate of subsequent formation of non-transient ATI (odds ratio, 4.66 [95% CI, 1.57-13.86]; P=.006) and shorter survival in the absence of nontransient ATI (P<.001).

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Antibodies to Adalimumab Predict Inflammation in Crohn's Patients on Maintenance Adalimumab Therapy

Filip J. Baert, Steven Lockton, Scott Hauenstein, Sharat Singh, Ann Gils, and Severine Vermeire

Although numerous studies have demonstrated the relationship between ATI and loss of response, the case for adalimumab has been less well described.[1] In an observational study of 168 CD patients who had presented with an initial response to infliximab but became intolerant or lost response, two-thirds of these patients demonstrated a response to adalimumab by week 12, and 61.5% exhibited a sustained clinical benefit through the end of a median 2 years of follow-up.[2] In a poster presented at Digestive Disease Week 2014, Filip Baert, MD, and colleagues provided data from additional analyses on the same study cohort examining the relationship between serum concentrations of adalimumab, ATA, and CRP.[3] The prospectively collected samples (N=536) were taken from 148 patients with a median age of 24 years (range, 19-30 years). Levels of serum adalimumab and ATA were measured at prespecified time points using the high mobility shift assay (HMSA), as previously described.[4] Samples were classified into 3 categories based on the results: ATA negative (no detectable signal); ATA detectable (detectable signal but below the lower limit of quantification [LLoQ] of 1.7 U/mL); and ATA positive (signal at or above the LLoQ). ATA measurements were positive in 30 patients (20.2%) after a median 34 weeks (interquartile range, 12.4-60.5 weeks). Compared with samples in the highest 2 quartiles of adalimumab level, samples in the lowest 2 quartiles were more often ATA-positive (P<.001; Figure 3). ATA-positive and ATA-detectable samples were associated with lower median adalimumab levels than ATA-negative samples (P<.001). The risk of future ATA formation was significantly increased in patients with adalimumab levels below 5 µg/mL at week 4 vs patients with higher adalimumab levels (HR, 11.13; P=.0002). CRP was negatively correlated with adalimumab levels (P=.0013) and positively correlated with ATA levels (P=.042). ATA level was significantly associated with a future CRP increase (P=.002), and median CRP was significantly higher in patients who eventually failed adalimumab therapy vs those who did not (8.34 mg/L vs 4.35 mg/L; P=.026). ATA-positive patients had a significantly higher likelihood of loss of response to adalimumab (odds ratio, 3.06 [95% CI, 1.04-9.09]; P=.034).

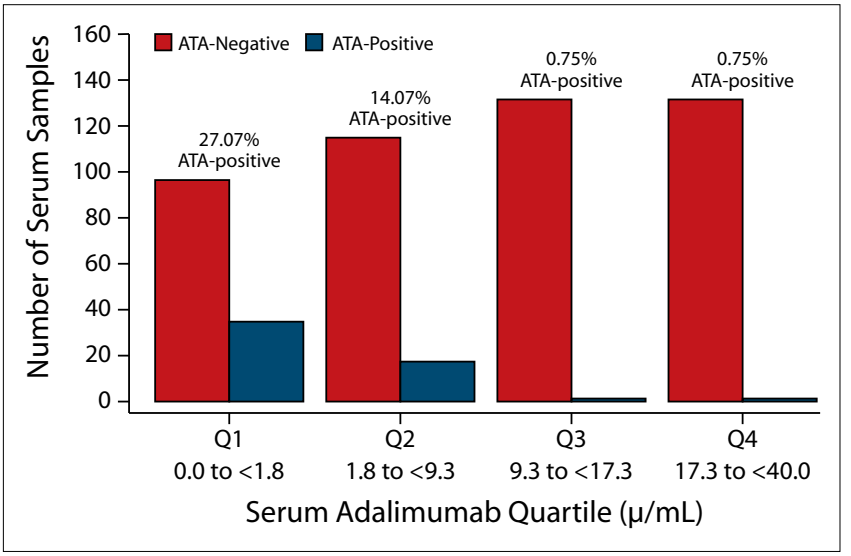

Figure 3. Compared with samples in the highest 2 quartiles of adalimumab level, samples in the lowest 2 quartiles were more often ATA-positive. Adapted from Baert FJ et al. DDW abstract Sa1247. *Gastroenterology*. 2014;146(suppl 1):S242.[3]

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ATG16L1 Genotype Is Associated With Response to Anti-TNF

Manon E. Wildenberg, Alon D. Levin, Johannan F. Brandse, Jessica R. de Bruyn, Geert R. D'Haens, and Gijs R. van den Brink

In the mixed lymphocyte reaction culture, the addition of infliximab induces macrophages with immunosuppressive and wound healing properties.[1] These regulatory macrophages appear to be involved in mucosal healing, and their number increases significantly in the intestines of patients who respond to infliximab.[2] Autophagy has been implicated in the development of CD, and studies show a relationship between certain autophagy genes and the development of CD. For example, the *ATG16L1* autophagy gene is associated with CD, and a single nucleotide polymorphism that results in the T300A mutation has been shown to decrease autophagy.[3] In a poster presented at Digestive Disease Week 2014, Manon Wildenberg, PhD, and coworkers described results from an investigation to determine whether autophagy is involved in the induction of regulatory macrophages by infliximab and whether polymorphisms in genes that govern autophagy influence the response to infliximab.[4]

Peripheral blood mononuclear cells (PBMC) were isolated from 29 healthy volunteers, and the allele status of ATG16L1 was determined. Mixed lymphocyte reaction cultures containing the PBMC from 2 donors were established for 150 different donor combinations. Cultures were incubated with infliximab or a control antibody for 6 to 7 days. Regulatory macrophages induced by infliximab displayed increased numbers of autophagosomes and increased expression of genes related to autophagy, including atg5, atg7, atg9, and atg1612. Seven PBMC donors were homozygous for the CD-associated risk allele in the ATG16L1 gene, 14 were heterozygous, and 7 carried the wild-type allele only. The number of CD14-positive regulatory macrophages correlated significantly with the total number of wild-type alleles represented by the donors in each mixed lymphocyte reaction culture. The total number of wild-type alleles in each culture also correlated positively with expression of CD206, a receptor associated with the immunosuppressive function of macrophages. Infliximab-mediated suppression of T-cell proliferation was determined and also demonstrated a significant, positive correlation with the number of wild-type alleles present in the respective donor combinations. The results suggest that induction of autophagy may play a role in the efficacy of anti-TNFα antibodies, such as infliximab.

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Highlights in Anti-Tumor Necrosis Factor Monitoring and Antibody Monitoring From the 2014 DDW Meeting: Commentary

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Monitoring of anti-tumor necrosis factor (TNF) drugs, such as infliximab or adalimumab, and antibodies to these drugs is most often used in patients with inflammatory bowel disease who have lost a previous response to a TNFα inhibitor. There is a growing body of evidence supporting this use, and monitoring is poised to become a routine part of clinical practice.[1,2] Two commercial homogeneous mobility shift assays (HMSA) are available: one for infliximab (Prometheus® Anser™ IFX) and one for adalimumab (Prometheus® Anser™ ADA).[1,3] The test results show whether a patient has developed anti–drug-antibodies that may be leading to rapid clearance of the drug. Drug and anti–drug-antibody monitoring provides information that may help physicians understand why patients are not responding to treatment or why they might be experiencing side effects.

There is an increasing understanding that the rate of drug clearance differs among patients—even in the early phases of disease—based on factors such as inflammatory burden, albumin, and body weight. Differences in these parameters result in variations in drug exposure that may then alter efficacy. The optimum drug levels that should be achieved early in the course of treatment with anti-TNFα therapy are still being defined. The indications are that an initial nonresponse to therapy probably indicates fast clearance of the drug, leading to not enough drug, rather than being indicative of a different mechanism of disease that is not responsive to anti-TNFα therapy.

Diagnostic testing, including drug monitoring, should not be performed unless the results have the potential to influence clinical management. The monitoring test results suggest a course of action, which may be to continue the drug unaltered, to escalate the dose, to withdraw the drug, or to de-escalate the dose. The testing is meant to rationalize therapy and allow for a more personalized approach to dosing. Among patients receiving biologic treatment, empirical dose escalations based on recurrent or persistent symptoms are unnecessary in up to 50%.[4-6] In some cases, persistent symptoms may be attributable to conditions other than active IBD or high levels of TNF. Biologic therapies are powerful medications with some inherent risks, and they are costly. Therefore, avoiding unnecessary dose escalation not only reduces the risk to patients but is also cost-effective. The pharmacoeconomic benefit associated with monitoring may be an important element in managing health care costs for IBD patients. A modeling analysis suggested that monitoring can significantly reduce drug costs,[7] and recent clinical trials have shown that optimizing drug levels was cost-effective without a loss of clinical efficacy.[8,9]

Monitoring in Other Clinical Settings

Monitoring of drug and anti–drug antibodies has generally been used in the setting of a secondary loss of response to the drug. However, such testing may also provide valuable information in other clinical situations. Patients who are being re-treated with infliximab or adalimumab after a drug holiday are at greater risk of developing antidrug antibodies; the presence of antibodies during re-treatment can be an indication that this approach will be unsuccessful.[10] Another setting in which monitoring may be clinically valuable is in patients who develop adverse events that could be immune-related and possibly associated with the anti-TNF agent, such as arthritis. Finally, some evidence suggests that patients may benefit from routine testing at the end of induction, and at some periodic time points during maintenance,[11] in order to confirm that the drug concentration is optimal and there are no antidrug antibodies. The data for the value of monitoring in these situations is intriguing, but additional information to support the clinical utility of the testing is required.

Endoscopic Healing

Observational data, population-based cohort data, and clinical trial data are increasingly showing that patients who achieve endoscopic healing have a better prognosis in both the ulcerative colitis and Crohn's disease settings.[12-14] A better prognosis means less disease progression, decreased formation of strictures and fistula abscess, less hospitalization, and fewer surgeries. It is debatable whether endoscopic healing is the right benchmark, or whether the goal should be histologic healing, especially in ulcerative colitis. So far, the data are more tentative for histologic healing than for endoscopic healing.[15]

DDW Abstracts

Classification of IBD has been based on serology and, to a lesser extent, gene markers. A study by Lockton and col-

leagues aimed to determine whether use of multiple markers would improve classification of IBD in a cohort of young patients, either by identifying conditions that are distinct from IBD or by differentiating ulcerative colitis from Crohn's disease.[16,17] The study showed that a combination of serologic, genetic, and inflammatory markers could improve the accuracy of an IBD diagnosis to 86%, with a negative predictive value of 65% and a positive predictive value of 96%. According to these results, if a patient tests positive for IBD, the accuracy of the diagnosis is high. However, with a negative test result, the patient may be positive in approximately one-third of cases. A positive IBD test is usually confirmed with further assessment, such as endoscopy. If a patient tests negative, but clinical suspicion is high, further assessment is also indicated. The numbers were similar for ulcerative colitis and Crohn's disease. For ulcerative colitis, the negative predictive value was 96%, and the positive predictive value was 68%. For Crohn's disease, the values were 74% and 93%, respectively.

This study of additional markers shows that there is a progressive ability to distinguish types of disease. These results will need to be confirmed in another study. It is unknown at which point a multimarker diagnostic panel will be able to replace other diagnostic modalities. However, this method is of increasing value as an adjunctive test to conventional modalities.

A study by Ferrante and coworkers examined the value of various clinical and serologic factors in predicting postoperative recurrence in patients with Crohn's disease.[18] Smoking, antiflagellin antibodies (anti-Fla2), and atypical perinuclear antineutrophil cytoplasmic antibodies (pANCA) were all strongly associated with endoscopic postoperative recurrence. A higher number of risk factors corresponded to a higher rate of recurrence. The finding is interesting because most patients will have a recurrence of their disease after surgery, and up to 60% of patients with Crohn's disease will eventually require surgery.[19] Without risk stratification, clinicians must choose between 2 management approaches after surgery: prophylactically treating all patients, including those who do not need it; or withholding treatment, including from some patients who do need it. This study has identified clinical variables associated with recurrence. These risk factors, if confirmed, could be useful clinical tools when determining which patients undergoing surgery should be treated afterward.

A study by Leclerc aimed to determine whether the presence of antidrug antibodies predicted loss of response.[20] The study enrolled 93 patients with ulcerative colitis or Crohn's disease who were treated with infliximab. Patients with antidrug antibodies persisting for 2 months or longer were at high risk of losing response. In patients with so-called *transient antibodies*, who have test results that are positive at some points and negative at others, the relationship was less clear. The study did not report whether the transient nature of antibody levels could be attributable to factors such as dose escalation of the drug or the addition of an immunosuppressant. Other studies have suggested that in patients with transient antibodies, the addition of an immunosuppressant or dose escalation of the drug accounts for antibody disappearance in up to 40%.[11] At a population level, it is not yet known whether it would be more cost-effective for patients with antibodies—even as shown with a single test—to switch drugs or to dose escalate. This study suggests that persistent antibodies are clinically important, and when present, the patient should probably switch drugs. The study's findings on transient antibodies are more difficult to interpret, and more data are required to understand the implications of this situation.

The combination of infliximab and a thiopurine immunosuppressant such as azathioprine has been shown to be more effective for IBD patients than either drug alone.[21] Thiopurines are metabolized to the active moiety, 6-thioguanine nucleotide (6TGN), and blood levels of 6TGN equal to or greater than 232 pmol/8 × 10^8 red blood cells have been associated with therapeutic benefit in IBD patients taking a thiopurine alone.[22] A study by Yarur and associates investigated the correlation among levels of 6TGN, infliximab, and ATI in patients on maintenance combination therapy.[23] They found that there was not a correlation between the dose of the thiopurine and infliximab, but that blood levels of 6TGN and infliximab were correlated, and that a 6TGN level of greater than 125 pmol/8 × 10^8 red blood cells predicted higher infliximab levels. Thus, when used in combination with infliximab, lower levels of 6TGN may provide significant clinical benefit with less toxicity.

A study by Ungar and coworkers examined the clinical and immunologic significance of low-level infliximab in the absence of ATIs.[24] This study found that the double-negative result is frequently due to false negative detection of ATI or infliximab by standard ELISA testing. In addition, if dosing is continued in the so-called double-negative patients, these patients will develop ATI at a high rate over time. This finding was expected, but still interesting to see in a clinical study.

In a study by Baert and associates, antibodies to adalimumab were associated with low drug concentrations, higher CRPs, and higher rates of nonresponse and relapse.[25] These data confirm those already seen with infliximab.[26-28] If the low drug levels are identified early, it may be possible to adjust dosing to prevent the development of antibodies to adalimumab, a rise in CRP, and, ultimately, clinical relapse. Although this observational study does not prove the value of therapeutic drug monitoring in a preemptive way, it suggests that routine, prospective monitoring of patients can

identify those who would benefit from an adjustment in therapy.

A similar study by Vaughn and coworkers focused on a single practice in which some of the physicians were routinely measuring drug concentrations early in the course of therapies and others were not.[29] The study found that when proactive measurement of drug levels identified low concentrations, even in patients without symptoms, dosage escalation permitted a longer course of therapy than when drug monitoring was performed in the reactive setting. This approach must be confirmed with a randomized controlled trial, but the study suggests that early monitoring could make the use of anti-TNFα agents much more effective.

A study by Wildenberg and colleagues focused on the impact of genes associated with autophagy on response to anti-TNFα therapy.[30] It showed that patients who have a polymorphism in the autophagy gene that may be involved in the pathway leading to ulcerations are not responsive to anti-TNF therapy. Although these data are preliminary, they suggest that response to anti-TNF therapy might require an intact autophagy pathway.

Conclusion

The 2014 DDW was a very interesting meeting for practitioners treating patients with IBD. Studies continue to expand the utility of monitoring in patients receiving anti-TNF therapy. Previous data have shown that monitoring is useful in patients who have lost response. New studies are now providing insight into how monitoring can be used in a much larger group of patients to optimize therapy earlier in the course of management so as to prevent loss of response.

Acknowledgment

Dr Sandborn is a consultant for Prometheus Laboratories, Janssen, and AbbVie. He has received research support from Prometheus Laboratories and AbbVie.

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