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Highlights in Anti–Tumor Necrosis Factor Monitoring

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Special Reporting on:

- Novel Infliximab and Antibody-to-Infliximab Assays Are Predictive of Disease Activity in Patients with Crohn's Disease
- Antibodies to Infliximab Can Either Be Persistent or Transient: A Retrospective Case-Control Study in IBD Patients Treated with Infliximab Maintenance Therapy
- Putting It Together: Drug Levels and Disease Activity to Tailor Therapy
- Infliximab Concentration and Clinical Outcome in Patients with Ulcerative Colitis

PLUS Meeting Abstract Summaries

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Table of Contents

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Novel Infliximab (IFX) and Antibody-to-Infliximab (ATI) Assays Are Predictive of Disease Activity in Patients with Crohn's Disease (CD)

Several theories have been proposed to explain why Crohn's disease (CD) patients lose response to infliximab; low trough infliximab levels and the development of antibodies to infliximab (ATIs) are 2 of the most widely such studied hypotheses. In 1 study of infliximab-treated CD patients, those with a loss of response had significantly lower infliximab trough levels (median, 0 µg/mL) and significantly higher ATI levels (median, 35 U/mL) compared to patients who maintained response (median infliximab level, 2.8 µg/mL; median ATI level, 0 U/mL; *P*<.0001 for both comparisons).[1] A separate study of 105 CD patients showed that ATIs were detectable in 21% of patients after a median of 14 infusions. Further, the rate of clinical remission with infliximab treatment was higher among individuals with detectable versus undetectable trough serum infliximab levels (82% vs 6%; *P*<.001). Detectable trough serum infliximab levels were also significantly associated with lower C-reactive protein (CRP) levels (2 µg/L vs 11.8 µg/L; *P*<.001).[2] Thus, monitoring both infliximab trough levels and ATI levels may help to guide infliximab dose adjustment and clinical decision-making in order to optimize patient outcomes.

Several methods are available to measure infliximab trough and ATI levels. These methods include solid-phase enzyme-linked immunosorbent assay (ELISA), bridging ELISA, and radioimmunoassay. However, the utility of these assays is limited by their inability to accurately measure ATI levels in the presence of infliximab. At the 2012 Digestive Disease Week (DDW) meeting held May 19–22, 2012 in San Diego, California, Severine Vermeire presented results showing that a novel homogeneous mobility shift assay can measure both ATI levels and infliximab trough levels without interference between the drug and the antibody.[3]

This assay uses a fluorescently labeled version of infliximab, which is incubated in serum from an infliximab-treated CD patient. During this incubation period, the labeled infliximab complexes with any ATIs present in the sample. Following equilibration, both the labeled infliximab and the ATI-bound labeled infliximab complex are resolved by size exclusion high performance liquid chromatography (HPLC), with the latter complex displaying a later peak due to its larger size. The ratio of these 2 unique peaks results in the mobility shift.

This mobility shift assay was used to evaluate the association between infliximab trough levels, ATI levels, and disease activity (as assessed by CRP levels) in infliximab-treated CD patients. A total of 1,487 serum samples from 483 CD patients were analyzed; all patients had received maintenance infliximab therapy during 1 of 4 studies: (1) the COMMIT trial, a randomized controlled trial designed to evaluate the effect of an immunomodulator on maintenance infliximab therapy; (2) a cross-sectional Canadian study that investigated the loss of response to infliximab; (3) a cohort trial that assessed the effect of infliximab dosing on ATIs; and (4) a second cohort trial that studied the withdrawal of concomitant immunomodulator therapy in patients treated with infliximab and an immunomodulator. All serum samples were obtained while the patients were on maintenance treatment. Approximately two thirds (64%) of patients had infliximab trough levels of 3 µg/mL or higher, and nearly one quarter (24%) of patients were ATI-positive. Because patients were on maintenance infliximab treatment, their disease was relatively well controlled; the median CRP level was 3.56 µg/L.

Using the mobility shift assay, both infliximab trough levels and ATI levels were measured. The majority of samples (72%) had high infliximab trough levels and no detectable ATIs. In contrast, only a small minority of samples (3.7%) had undetectable trough infliximab levels and no detectable ATIs. The remaining patients either had undetectable trough levels and detectable levels of ATIs (13.4%), or they had detectable infliximab trough levels and detectable ATI levels (10%). These data were used to construct a receiver operating characteristic (ROC) curve, which showed that an infliximab cutoff of 3 µg/mL could accurately predict CD activity as measured by CRP level.

Among ATI-negative patients, the median CRP level was significantly lower in those individuals who had high infliximab trough levels. However, this inverse correlation was lost among ATI-positive patients, who showed high median CRP levels regardless of infliximab trough level. Multivariate analysis confirmed that both infliximab trough level and ATI status could independently predict CRP level. Infliximab trough levels negatively correlated with CRP levels, with the median CRP level being 52% lower in patients with an infliximab trough level of 3 µg/mL or higher compared to patients with an infliximab trough level below 3 µg/mL. ATI levels also correlated with CRP: In patients with an infliximab trough level below

ABSTRACT SUMMARY New Assay to Detect Infliximab Levels and Anti-Infliximab Antibodies From a Single Serum Sample Is Useful in Measuring Efficacy of Treatment with Infliximab in Children with IBD

The most widespread method for detection of ATIs is a double-antigen ELISA, which uses infliximab as both the ligand and the detection antibody. However, this assay is limited by its inability to accurately determine ATI levels in the presence of serum infliximab concentrations. In a poster presented at the 2012 DDW meeting, Gabor Veres and colleagues reported on the development of a novel homogeneous mobility shift assay and demonstrated that it could detect both infliximab and ATIs in the same serum sample.[1]

The homogeneous mobility shift assay uses fluorescently labeled infliximab, which has a molecular weight of approximately 150 kD. This labeled infliximab is incubated in serum from infliximab-treated patients, and the labeled infliximab forms complexes with any ATIs that may be present in the sample. The large fluorescently labeled infliximab-ATI complex has a distinct peak when subjected to HPLC. Similarly, fluorescently labeled tumor necrosis factor α (TNF-α) is also added to infliximab-treated serum; after incubation, this labeled TNF-α will be bound to any infliximab present in the sample. Again, the resulting immunocomplex has a high molecular weight and a distinctive peak by HPLC.

This novel homogeneous mobility shift assay was used to measure serum infliximab concentrations and ATI levels in 230 serum samples from 71 pediatric inflammatory bowel disease (IBD) patients. A subset of these children (n=31) also had 6 serial trough infliximab measurements, each taken prior to an infusion. A 5 mg/kg induction dose of infliximab was administered at Weeks 0, 2, and 6, followed by maintenance dosing every 8 weeks.

ATIs were detected in 20.4% of the serum samples (range, 0.28–800+ U/mL) and in 29.6% of the 71 children. Of the 47 ATI-positive serum samples, 8 also demonstrated measurable infliximab serum concentrations (range, 0.77–19.27 µg/mL). In the subset of children with serial trough level measurements, 8 had ATI-positive serum samples. Among ATI-positive samples, the median infliximab serum concentration was 0 µg/mL; in contrast, the median infliximab serum concentration among ATI-negative samples was 2.55 µg/mL (P<.0001). None of the ATI-positive samples exhibited infliximab serum concentrations of 3 µg/mL or higher, while 45% of the ATI-negative samples had infliximab levels of 3 µg/mL or higher. ATI-positive patients also had CRP levels that were approximately 1.5-fold higher than CRP levels in ATI-negative patients. A linear regression model found that a majority (88%) of children in the subset of patients with serum infliximab concentrations of 3 µg/mL or higher showed a decrease in CRP levels.

In conclusion, the investigators showed that ATI positivity may be a predictor of lower infliximab levels and increased CRP levels in pediatric IBD patients. As expected, higher infliximab levels (≥3 µg/mL) correlated with lower CRP levels. Importantly, this novel homogeneous mobility shift assay allowed simultaneous detection of serum infliximab concentrations as well as ATIs.

Reference

1. Veres G, Kaplan JL, De Greef E, et al. New assay to detect infliximab levels and anti-infliximab antibodies from a single serum sample is useful in measuring efficacy of treatment with infliximab in children with IBD. Presented at Digestive Disease Week; May 19–22, 2012; San Diego, California. Abstract Sa2037.

3 µg/mL, the median CRP level was higher among ATI-positive patients compared to ATI-negative patients (8.4 µg/L vs 5.65 µg/L, respectively; P<.001). The same trend was observed in patients with an infliximab trough level of 3 µg/mL or higher (9.9 µg/L for ATI-positive patients vs 1.5 µg/L for ATI-negative patients; P<.01).

Based on these results, the investigators concluded that this novel homogeneous mobility shift assay could accurately measure both infliximab trough levels and ATI levels without the interference that limits other currently used assays. Using the homogeneous mobility shift assay, they confirmed that CRP levels were strongly associated with infliximab trough levels. Further, this study was the first to demonstrate that CRP levels were higher among ATI-positive patients versus ATI-negative patients independent of infliximab trough levels; this finding contradicts the previously held theory that ATI positivity would not predict high CRP levels as long as infliximab trough levels remained sufficiently high. Further study is required to determine the best strategy for management of patients who lose response to infliximab and/or develop ATIs in the setting of sufficiently high trough infliximab levels.

References

1. Steenholdt C, Bendtzen K, Brynskov J, Thomsen OØ, Ainsworth MA. Cut-off levels and diagnostic accuracy of infliximab trough levels and anti-infliximab antibodies in Crohn's disease. *Scand J Gastroenterol.* 2011;46:310-318.

2. Maser EA, Villela R, Silverberg MS, Greenberg GR. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. *Clin Gastroenterol Hepatol.* 2006;4:1248-1254.

3. Feagan BG, Singh S, Lockton S, et al. Novel infliximab (IFX) and antibody-to-infliximab (ATI) assays are predictive of disease activity in patients with Crohn's disease (CD). Presented at Digestive Disease Week; May 19–22, 2012; San Diego, California. Abstract 565.

Antibodies to Infliximab Can Either Be Persistent or Transient: A Retrospective Case-Control Study in IBD Patients Treated with Infliximab Maintenance Therapy

Infliximab is a chimeric mouse-human immunoglobulin (Ig) G1 monoclonal antibody directed against the proinflammatory cytokine TNF-α. Despite its proven efficacy in the treatment of IBD, infliximab therapy can result in an immunogenic response in which the immune system develops ATIs. Patients who develop ATIs during infliximab therapy often have a worse prognosis, and significant ATI formation has been linked to a loss of clinical benefit with infliximab.[1] Further, the development of ATIs has been linked to the occurrence of either acute or delayed hypersensitivity reactions, as well as other adverse events.

One potential explanation why response to infliximab may sometimes be restored is that ATIs may exhibit a transient characteristic when they are present at low levels. To investigate this hypothesis in more detail, Niels Vande Casteele presented a retrospective case-control study that evaluated the formation and persistence of ATIs in consecutive serum samples from IBD patients.[2] This presentation was given during the 2012 DDW meeting.

Ninety IBD patients were identified from the VLEEC registry between 1999 and 2011; a total of 1,232 trough serum infliximab samples were available from these patients. Patient selection was based on detection of ATIs by ELISA; a control population (n=37) consisting of patients who never developed ATIs was also selected (termed the ATI-negative group). All samples were retrospectively analyzed using a homogeneous liquid-phase mobility shift assay to determine trough infliximab levels and ATI levels. As this was a retrospective study, all decisions to optimize or stop infliximab therapy were based on clinical considerations and CRP levels, without any knowledge of trough infliximab levels or ATI levels.

Of the 53 patients who developed ATIs, 15 exhibited a loss of ATIs over time, while the remaining 38 patients showed consistently detectable ATI levels; these groups were termed the ATI-transient and ATI-sustained groups, respectively. Despite this study having a different number of patients in each ATI group, the average number of serum samples per patient was similar across all 3 groups.

At the time of initiation of infliximab, the median CRP level was significantly higher among patients who later developed detectable ATI levels than those who did not. The development of ATIs occurred a median of 16 weeks following the start of infliximab therapy (interquartile range [IQR], 8–39 weeks), which correlated with a median of 4 infusions (IQR, 3–6 infusions). There was no difference between the ATI-transient and ATI-sustained groups in terms of the time to development of ATIs. However, there was a significant difference in the duration of detectable ATI levels, with detectable ATI levels being present for a median duration of 17 weeks (IQR, 9–60 weeks) and 45 weeks (IQR, 20–115 weeks) in the ATI-transient and ATI-sustained groups, respectively. This difference correlated with the median number of infliximab infusions (3 vs 5 in the ATI-transient vs ATI-sustained groups, respectively).

The median ATI level at the first ATI-positive time point was 15 U/mL in both the ATI-transient and ATI-sustained groups. Patients in the ATI-sustained group developed significantly higher levels of ATIs compared to patients in the ATI-transient group. A ROC analysis of ATI levels at the time of dose adjustment (T0) showed that an ATI level above 9.4 U/mL gave a 72% specificity, a 70% sensitivity, and a likelihood ratio of 2.5 for unsuccessfulness of the intervention (area under the curve=0.800; standard error=0.07; P=.0004).

During the follow-up period, 53 of the 90 patients lost clinical response to infliximab. In 49 of these patients, an infliximab dose adjustment was attempted. Of these 49 patients, 36 had an interval decrease, 6 had a dose increase, and 7 had both an interval decrease and a dose increase. Dose adjustment in patients who developed ATIs was clinically unsuccessful in 47% of patients (n=23).

The influence of infliximab dose adjustment on trough infliximab levels was determined at the time of dose adjustment (T0) and at 2 subsequent time points (T1 and T2). Patients in whom dose adjustment was successful showed a significant increase in trough infliximab levels compared to patients who did not have a successful response to dose adjustment, in whom no increase in trough infliximab levels was observed. When the impact of ATI status on outcome to dose adjustment was evaluated, ATI positivity at the time of dose adjustment was a risk factor for a poor outcome (relative risk, 2.7).

A total of 28 patients required infliximab discontinuation due to loss of response (n=20) or hypersensitivity reactions (n=8). Of the 38 patients in the ATI-sustained group, inflix-

ABSTRACT SUMMARY Comparison of Homogeneous Mobility Shift Assay and Solid-Phase ELISA for the Measurement of Drug and Anti-Drug Antibody (ADA) Levels in Serum From Patients Treated with Anti-TNF Biologics

The development of antibodies to biologic therapies is not limited to infliximab. Indeed, development of antibodies against adalimumab and other anti–TNF-α agents is a frequent side effect of treatment. Generation of these antidrug antibodies is associated with both loss of drug effectiveness and occurrence of adverse events.

Solid-phase ELISAs are one of the methods most commonly employed to detect both anti–TNF-α antibodies and antidrug antibodies. However, these ELISAs have a limited ability to detect antidrug antibodies in serum samples that contain significant concentrations of the drug. To overcome these limitations, a homogeneous mobility shift assay was developed that can simultaneously measure the concentrations of both the antidrug antibodies and the drug present in a serum sample. The homogeneous mobility shift assay is capable of detecting any anti–TNF-α biologic therapy, and it can be optimized to improve sensitivity as well as dynamic range.

In a poster presented at the 2012 DDW meeting, Scott Hauenstein and colleagues reported on the ability of this novel homogeneous mobility shift assay to measure levels of infliximab and ATIs, as well as levels of adalimumab and antibodies to adalimumab.[1] These results were compared with ELISA, which is the current standard for measurement of drug and antidrug antibody levels.

Using the homogeneous mobility shift assay, ATI levels were shown to dilute linearly in the presence of both 14 µg/mL and 60 µg/mL doses of infliximab. In contrast, the ELISA assay did not consistently detect ATIs in the presence of infliximab. Likewise, the infliximab homogeneous mobility shift assay determined accurate values for infliximab serum concentrations even in the presence of up to 10 µg/mL of ATI, outperforming ELISA across all concentrations. The ATI homogeneous mobility shift assay remained linear between 0.56–30 µg/mL of ATI, while the ATI ELISA overestimated the amount of ATI at low concentrations and was unable to accurately detect high levels of ATIs. Overall, both the homogeneous mobility shift assay and ELISA were able to detect infliximab, but the homogeneous mobility shift assay proved to be more accurate.

Using the adalimumab version of the homogeneous mobility shift assay, 81 adalimumab-treated IBD patients and 23 healthy controls were evaluated. The mean adalimumab concentration was found to be 16.5 µg/mL (range, 1.3–70.9 µg/mL).

Based on these results, the investigators concluded that the homogeneous mobility shift assay readily detected both anti–TNF-α agents and the autoantibodies directed against these agents, which can be produced by a patient's immune system during treatment. This assay is unique because it can detect antidrug antibody levels even in samples with high drug concentrations; this property may make such testing useful for monitoring antibody concentrations in patient samples in real time, as it could facilitate dose adjustments that might help to optimize outcomes.

Reference

1. Hauenstein S, Ohrmund L, Salbato J, et al. Comparison of homogeneous mobility shift assay and solid-phase ELISA for the measurement of drug and anti-drug antibody (ADA) levels in serum from patients treated with anti-TNF biologics. Presented at Digestive Disease Week; May 19–22, 2012; San Diego, California. Abstract Su1928.

imab was discontinued due to loss of response or hypersensitivity reactions in 19 patients (50%) and 7 patients (18%), respectively. Only 9 of the 38 patients in the ATI-sustained group continued infliximab therapy. Analysis showed that patients who developed sustained ATIs had a relative risk of 1.9 for infliximab discontinuation due to loss of response or hypersensitivity reactions.

The study authors concluded that IBD patients who developed ATIs were more likely to discontinue infliximab due to loss of response or hypersensitivity reactions. In addition, patients who were ATI-positive at the time of loss of response were significantly less likely to respond successfully to an infliximab dose adjustment.

References

1. Maser EA, Villela R, Silverberg MS, Greenberg GR. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. *Clin Gastroenterol Hepatol*. 2006;4:1248-1254.
2. Casteele NV, Cuypers L, Singh S, et al. Antibodies to infliximab can either be persistent or transient: a retrospective case-control study in IBD patients treated with infliximab maintenance therapy. Presented at Digestive Disease Week; May 19–22, 2012; San Diego, California. Abstract 563.

Putting It Together: Drug Levels and Disease Activity to Tailor Therapy

In another presentation at the 2012 DDW meeting, William Sandborn discussed how to tailor therapy to disease activity.[1] In this context, Sandborn reviewed how both drug levels and disease activity could be incorporated into clinical decision-making.

Research has previously established that high levels of immunogenic antibodies directed against anti–TNF-α agents are associated with an attenuated response to biologic therapy or a hypersensitivity reaction. The clinical significance of these anti–TNF-α antibodies in affecting response to treatment was first established in a cohort study of 125 consecutive CD patients who were treated with standard-dose infliximab induction therapy (mean of 3.9 infusions; range, 1–17) over a mean of 10 months.[2] More than half (61%) of patients exhibited detectable levels of ATIs. Patients with ATI levels of 8 µg/mL or higher prior to an infusion had a significantly shorter duration of response compared to patients with ATI levels below 8 µg/mL (35 days vs 71 days; *P*<.001). Further, patients with ATI levels of 8 µg/mL or above had a heightened risk of infusion reactions (relative risk, 2.40; 95% confidence interval, 1.65–3.66; *P*<.001).

At Week 4, the concentration of infliximab was significantly lower in patients who had experienced an infusion reaction compared to patients who had never had an infusion reaction (median, 1.2 µg/mL vs 14.1 µg/mL; *P*<.001). Infusion reactions also correlated significantly with clinical response, with a median duration of clinical response of 38.5 days in patients with an infusion reaction versus 65 days in patients who did not experience an infusion reaction (*P*<.001). Finally, the use of concomitant immunosuppressive therapy was found to be predictive of lower ATI titers (*P*<.001) as well as high infliximab concentrations 4 weeks after an infusion (*P*<.001).

This study was quickly followed by a confirmatory report, which found that 36% of 53 CD patients developed ATIs after infliximab administration.[3] Notably, the 7 patients in this study who experienced serious infusion reactions all had ATIs (median, 19.6 µg/mL). Nearly three quarters (73%) of the patients who lost response to infliximab were positive for ATIs, while none of the patients who maintained a continued response to infliximab were ATI-positive. A subsequent randomized controlled trial of 80 CD patients found that ATI levels at Week 16 were lower among patients who had been premedicated with intravenous hydrocortisone compared to those who received placebo (1.6 µg/mL vs 3.4 µg/mL; *P*=.02). Only 26% of patients in the hydrocortisone arm developed ATIs compared to 42% of placebo-treated patients (*P*=.06).

The SONIC trial, which compared the efficacy and safety of infliximab and immunomodulators either alone or in combination for the treatment of CD, also assessed the effect of therapy on ATIs.[5] At Week 30, ATIs were detected in 15 of 103 patients (14.6%) receiving infliximab monotherapy. Median trough serum infliximab levels at Week 30 were 1.6 µg/mL for patients in the infliximab monotherapy arm and 3.5 µg/mL for patients in the combination therapy arm (*P*<.001). Importantly, the rate of corticosteroid-free clinical remission was highest among patients with increased trough infliximab levels, but corticosteroid-free remission rates were also relatively high in patients with lower trough levels.

While these studies examined patients treated with infliximab, a similar correlation has been established between worse clinical response and the formation of antibodies directed against adalimumab.[4] Because adalimumab is a humanized antibody, these antibodies are referred to as human antihuman antibodies.

Other factors have also been found to affect treatment response. For example, low serum albumin levels are predictive of high drug clearance. Several mechanisms could explain this finding. One possibility is that low serum albumin levels may simply be a surrogate marker for high inflammatory burden and high TNF-α levels. Another potential explanation is that albumin and IgG1 antibodies compete for drug clearance through the reticular endothelial system via FcRn receptors. In the setting of low albumin, therefore, more FcRn receptors would be available to bind and clear the therapeutic antibody.

Finally, trough infliximab and adalimumab levels have repeatedly been shown to be an important determinant of clinical efficacy. A number of studies have shown that a trough drug concentration approaching 3 µg/mL is associated with improved clinical outcomes, including higher rates of mucosal healing and clinical remission. One interesting point to consider is how the drug's dosing schedule affects trough levels. Infliximab is dosed every 8 weeks during maintenance therapy, resulting in a high C_{max}; infliximab concentration then tapers off and dips down to a lower trough level. In contrast, adalimumab is dosed every 1–2 weeks during maintenance therapy, resulting in lower C_{max} peaks; because of the more frequent dosing, however, trough levels of adalimumab are generally higher.

ABSTRACT SUMMARY One Third of Patients Treated with Adalimumab or Infliximab for Crohn's Disease or Ulcerative Colitis Permanently Dose Escalate Due to Loss of Response

Despite the significant efficacy of infliximab and adalimumab for the treatment of IBD, many patients lose response to these drugs. In a poster presented at the 2012 DDW meeting, Darryl Fedorak and colleagues reported the findings of a retrospective chart review in which they sought to determine the incidence of loss of response among patients treated with either of these 2 agents.[1] They further evaluated these charts to determine how many patients required dose escalation.

The investigators identified 363 patients who met the inclusion criteria for this study. All enrolled patients had an initial response to induction dosing with either infliximab (5 mg/kg administered at Weeks 0, 2, and 6) or adalimumab (160 mg and 80 mg administered at Weeks 0 and 2, respectively). Patients also had to have advanced to scheduled maintenance therapy (every 8 weeks with infliximab or every 2 weeks with adalimumab), achieved a stable corticosteroid-free clinical benefit that was durable for a minimum of 6 months, and exhibited a loss of response to their anti–TNF-α therapy. Finally, enrolled patients had to have sufficient follow-up to allow assessment of ongoing wellness and/or disease relapse with dose-escalated treatment.

At the time of the analysis, 65% of infliximab-treated patients remained in remission while on infliximab maintenance therapy at a dose of 5 mg/kg infliximab every 8 weeks. Similarly, 72% of adalimumab-treated patients were in remission on maintenance therapy with 40 mg adalimumab every other week. Thirty-five percent of patients who received infliximab required dose escalation (to 5 mg/kg every 4 weeks). Twenty-eight percent of adalimumab-treated patients required dose escalation (to 40 mg weekly). There was no significant difference in the rates of dose escalation between ulcerative colitis (UC) and CD patients. Further, a Kaplan-Meier plot found no significant difference in the time to treatment failure between infliximab and adalimumab (Log-rank *P*=.56). Finally, dose de-escalation was uncommon. Only 7 infliximab-treated patients underwent dose de-escalation to the original doses; none of the adalimumab-treated patients underwent dose de-escalation.

Reference

1. Fedorak DK, Osatiuk P, Wong K, et al. One third of patients treated with adalimumab or infliximab for Crohn's disease or ulcerative colitis permanently dose escalate due to loss of response. Presented at Digestive Disease Week; May 19–22, 2012; San Diego, California. Abstract Sa2049.

Consideration of antidrug antibody levels and drug trough levels are important parts of clinical decision-making, as clinicians cannot always rely on clinical symptoms to tailor therapy. Often, the relationship between clinical symptoms and endoscopy is weak in CD, in part because a number of factors can cause symptoms in CD patients even when they are not experiencing a disease flare. These factors include the natural history of CD (strictures, fistulae, and abscesses), surgical complications, irritable bowel syndrome in the setting of CD, *Clostridium difficile* infection, and other comorbidities such as depression.

As a way of putting new research into practice, treatment algorithms can help clinicians take drug and antibody levels into consideration. For example, if a patient has a low drug level and no antibodies, the appropriate response would be to escalate the dose. In contrast, if a patient has low drug levels and antidrug antibodies, it may be necessary to switch to a different medication. Finally, for patients who show symptoms despite high concentrations of drug, the patient should be carefully assessed to determine whether there is mucosal healing and/or whether some other comorbidity could be accounting for the symptoms.

References

1. Sandborn WJ. Putting it together: drug levels and disease activity to tailor therapy. Presented at Digestive Disease Week; May 19–22, 2012; San Diego, California. Abstract Sp705.
2. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med*. 2003;348:601-608.
3. Farrell RJ, Alsahli M, Jeen YT, Falchuk KR, Peppercorn MA, Michetti P. Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: a randomized controlled trial. *Gastroenterology*. 2003;124:917-924.
4. Karmiris K, Paintaud G, Noman M, et al. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. *Gastroenterology*. 2009;137:1628-1640.
5. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med*. 2010;362:1383-1395.

Infliximab Concentration and Clinical Outcome in Patients with Ulcerative Colitis

The ACT-1 and ACT-2 studies were multicenter, randomized, double-blind, placebo-controlled trials that compared 5 mg/kg and 10 mg/kg doses of infliximab versus placebo for the treatment of moderate-to-severe UC.[1] Each study enrolled 364 patients between March 2002 and March 2005, and all patients had a Mayo clinic score of 6–12 points. Treatment was administered at Weeks 0, 2, and 6, followed by maintenance therapy every 8 weeks through Week 22 in ACT-2 and through Week 46 in ACT-1. The primary study endpoint was clinical response at Week 8; secondary endpoints included clinical response or remission with discontinuation of corticosteroids at Week 30 in both studies (and at Week 54 in ACT-1), clinical remission and mucosal healing at Weeks 8 and 30 in both studies (and at Week 54 in ACT-1), and clinical response at Week 8 in patients with steroid-refractory disease. In both studies, clinical response was defined as a decrease in the Mayo clinic score of at least 3 points and at least 30%, with an accompanying decrease of at least 1 point in the rectal bleeding subscore or an absolute rectal bleeding subscore of 0 or 1.

Significantly more patients in both the 5 mg/kg and 10 mg/kg infliximab groups achieved clinical response at Week 8 compared to patients in the placebo arm (69% and 61% vs 37%; $P<.001$ for both comparisons vs placebo). In both trials, infliximab-treated patients were more likely to achieve clinical response at Week 30 ($P\leq.002$ for all comparisons). ACT-1, which had a longer follow-up period, also showed that more of the patients treated with infliximab (either 5 mg/kg or 10 mg/kg) achieved a clinical response at Week 54 (45% and 44%, respectively) compared to patients who received placebo (20%; $P<.001$ for both comparisons).

Building on this research, a post–hoc analysis of the ACT-1 and ACT-2 studies was conducted to evaluate the association between serum infliximab concentrations and clinical outcomes in patients with moderately to severely active UC; Walter Reinisch presented results of this post–hoc analysis during the 2012 DDW meeting.[2] While the ACT studies examined 2 doses of infliximab, the post–hoc analysis only evaluated patients in the 5 mg/kg infliximab dosage group, as this is the dose that was approved by the US Food and Drug Administration as a treatment for UC.

Pharmacokinetic sampling was performed throughout the ACT-1

ABSTRACT SUMMARY The Prevalence of Human Antichimeric Antibodies in Patients on Infliximab Increases with Age

In another poster presented at the 2012 DDW meeting, David Barry and Richard S. Bloomfeld reported on a study in which they determined the prevalence of human antichimeric antibodies among infliximab-treated IBD patients and correlated the presence of these antibodies with patient age.[1] In this retrospective analysis, all human antichimeric antibody testing performed by Prometheus Laboratories between November 2000 and January 2011 was evaluated. A total of 26,450 patients were included in this analysis; individuals younger than 10 years and older than 80 years of age were excluded. Patients were divided into 7 age groups, with each group spanning a range of 10 years. A negative human antichimeric antibody result was defined as a serum concentration below 1.69 µg/mL, while a positive result was defined as a serum concentration above 1.69 µg/mL.

The proportion of patients with a negative human antichimeric antibody result decreased significantly with increasing patient age (Chi square; $P<.0001$). Of the 10,155 patients aged 10–19 years, 81.9% had a negative human antichimeric antibody result. This percentage decreased to 80% of 4,004 patients aged 20–29 years, 78.9% of 3,831 patients aged 30–39 years, 79.9% of 3,509 patients aged 40–49 years, and 79.9% of 2,735 patients aged 50–59 years. This number continued to decrease in older patients, with 77.8% of patients aged 60–69 years and 74.8% of patients aged 70–79 years having a negative human antichimeric antibody result.

Based on these data, the investigators concluded that human antichimeric antibodies increase in prevalence among older infliximab-treated IBD patients. This finding could have a significant impact on clinical decision-making in young versus older IBD patients who lose response to anti–TNF-α therapy.

Reference

1. Barry D, Bloomfeld RS. The prevalence of human antichimeric antibodies in patients on infliximab increases with age. Presented at Digestive Disease Week; May 19–22, 2012; San Diego, California. Abstract Sa2040.

ABSTRACT SUMMARY Association of Serum Infliximab and Antibodies to Infliximab to Long-Term Clinical Outcome in Acute Ulcerative Colitis

In a poster presented at the 2012 DDW meeting, Sanjay Murthy and colleagues used a newly developed homogeneous mobility shift assay to assess the relationships among trough infliximab levels, ATI levels, and long-term clinical outcomes in patients with acute UC.[1] A total of 134 patients with corticosteroid-refractory acute UC were included in this analysis; 103 patients had pancolitis, and 31 patients had disease limited to the splenic fixture. All patients had received 5 mg/kg infliximab induction therapy on Weeks 0, 2, and 6, followed by scheduled maintenance therapy. Corticosteroid-free remission (defined as a Mayo clinic score of 0) and colectomy were used as endpoints in this evaluation. At baseline, the median Mayo clinic score was 9 points (range, 6–12 points).

After a median follow-up period of 19.9 months (IQR, 7.6–7.4 months), 43.3% of patients were in corticosteroid-free remission, and 39.6% had undergone colectomy. The median time to colectomy was 6.5 months (IQR, 2.3–13.4 months). Among 125 patients with evaluable serum samples, 54.4% (n=68) had detectable trough levels of serum infliximab. Of these 68 patients, 6 patients (8.8%) also had detectable levels of ATIs. Of the 57 patients (45.6%) who had undetectable trough serum infliximab levels, 45 patients (78.9%) were ATI-positive, and 12 patients (21.1%) were ATI-negative.

Importantly, the investigators showed that a trough infliximab level of 2 µg/mL or higher was associated with a higher rate of corticosteroid-free remission compared to a trough infliximab level below 2 µg/mL (69% vs 16%; *P*<.001). This relationship was sustained throughout the follow-up period. In contrast, a trough infliximab level below 2 µg/mL was significantly associated with an increased risk for colectomy compared to a trough infliximab level above 2 µg/mL (64% vs 13%; *P*<.001).

Reference

1. Murthy S, Kevans D, Seow CH, et al. Association of serum infliximab and antibodies to infliximab to long-term clinical outcome in acute ulcerative colitis. Presented at Digestive Disease Week; May 19–22, 2012; San Diego, California. Abstract Sa2047.

and ACT-2 studies, most often at the time of an infusion, although samples were also taken at Week 8. By Week 8, the subset of UC patients who were responding to infliximab began to diverge from the group of patients who did not respond to infliximab. Interestingly, there was no significant difference in peak serum infliximab levels between the responding and nonresponding patients at this time point. In contrast, trough infliximab levels were lower in nonresponding patients versus responding patients.

Further analysis demonstrated that patients who achieved a clinical response at Week 8 had a serum infliximab concentration of 35 µg/mL, compared to a serum infliximab concentration of 25.8 µg/mL in patients who did not achieve a clinical response; this difference was statistically significant. Similarly, patients who achieved and did not achieve mucosal healing by Week 8 had serum infliximab concentrations of 36.1 µg/mL and 26 µg/mL, respectively; this difference did not achieve statistical significance.

At Week 30, trough infliximab concentrations were again higher among patients who achieved a clinical response compared to those who did not (5 µg/mL vs 1.2 µg/mL). Interestingly, there was a large amount of variability in serum infliximab concentrations between responders and nonresponders and between patients who achieved mucosal healing and those who did not. At the time of the Week 30 trough level measurement, this separation increased further. This finding could be attributed to the increased rate of drug clearance due to development of immunogenicity. When serum infliximab concentrations were divided into quartiles, Reinisch and colleagues found that there was an incremental increase in the likelihood of achieving clinical response or mucosal healing with each higher quartile of infliximab concentration; the same trends were shown for clinical remission at Weeks 30 and 54.

From this post–hoc analysis, the investigators concluded that serum infliximab concentrations began to diverge as early as Week 8 between patients who achieved an endpoint (either clinical response or mucosal healing) and those who did not. While the serum infliximab concentrations required to achieve response and maintain remission varied substantially among patients, higher serum infliximab concentrations were associated with a greater likelihood of achieving these endpoints. The investigators acknowledged that a prospective study is needed to determine whether adjustment of serum infliximab concentrations has clinical utility for optimizing patient outcomes.

References

1. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2005;353:2462-2476.
2. Reinisch W, Feagan BG, Rutgeerts PJ, et al. Infliximab concentration and clinical outcome in patients with ulcerative colitis. Presented at Digestive Disease Week; May 19–22, 2012; San Diego, California. Abstract 566.

Commentary

William J. Sandborn, MD

One of the major themes at the 2012 DDW meeting, which was held May 19–22, 2012 in San Diego, California, was the utility of measuring drug levels and/or antidrug antibody levels in IBD patients who are receiving anti-TNF therapy. While more research is needed to fully explore this area, the available data suggest that measuring drug and/or antibody levels could help clinicians to optimize anti-TNF therapy by adjusting drug doses or switching to alternative therapies in patients who are unlikely to respond to continued treatment with a particular agent. Several presentations that addressed this topic were summarized in the current monograph.

In a post–hoc analysis of the ACT-1 and ACT-2 studies, Reinisch and colleagues showed a strong relationship between serum infliximab concentrations and clinical response.[1] Interestingly, the original analyses of the ACT trials did not show a statistically significant difference in outcomes between patients treated with 5 mg/kg infliximab and those treated with 10 mg/kg infliximab; thus, it was assumed that clinicians were achieving optimal dosing with 5 mg/kg, which is the approved dose of infliximab for treatment of UC. However, more recent data indicate that drug clearance is influenced by a number of confounding factors, including gender, body weight, CRP level, serum albumin level, and concomitant immunosuppression. All of these factors drive significant interpatient variability in the clearance of infliximab, and in some cases, this variability is so great that it can overwhelm a doubling of the dose. Previously, data showed that approximately two thirds of patients responded to infliximab, and one third of patients achieved remission. With dose optimization, approximately 75–80% of patients can achieve a response, and 50% of patients can achieve remission.

A second major topic of the 2012 DDW meeting related to a new assay system that can measure both drug levels and antidrug antibody levels. Previously, ELISA-based assay systems could not accurately measure antidrug antibody levels if there was any infliximab present in the sample. With the development of chromatography-based assay systems, however, researchers and clinicians can now measure both drug levels and antidrug antibody levels at the same time, anytime during therapy.

By allowing researchers to measure even small amounts of antidrug antibodies, this assay system showed that the presence of antidrug antibodies is another factor that affects drug clearance. During the 2012 DDW meeting, Dr. Severine Vermeire also presented data showing that antidrug antibodies above a certain level were an independent predictor of high CRP levels in patients with CD, even in patients with detectable drug levels.[2] While the interaction between the drug and the antidrug antibodies is not yet fully understood, I suspect that the observed antidrug antibodies affected the maximum concentration of the drug and the area under the curve early in the 8-week dosing interval—before the trough drug concentrations were measured; this earlier impact could have changed the pharmacokinetics of the drug in a way that altered its clinical efficacy. Interestingly, this study also found that an infliximab cutoff of 3 µg/mL could predict CD activity as measured by CRP level; this threshold is very similar to the cutoff identified by Reinisch and colleagues for maintenance of remission in UC.

In a third talk that deserves mention, Dr. Niels Vande Casteele presented data showing that antidrug antibodies can be either persistent or transient.[3] While the sustained presence of antidrug antibodies was found to limit the efficacy of infliximab therapy, this therapy could still be successful if the antidrug antibodies were transient.

Finally, one study that was not included in this supplement but that still deserves a brief mention is the TAXIT study, a prospective study designed to assess the clinical impact of dose optimization.[4] The concept of dose adjustment based on drug levels has several potential benefits, one of which is that clinicians could not only increase drug doses in patients with subtherapeutic drug levels but could also reduce drug doses in patients with supertherapeutic levels. In the TAXIT trial, the researchers aimed to maintain infliximab trough concentrations in the range of 3–7 µg/mL during the maintenance phase of therapy; a group of patients in whom dose adjustments were based on drug levels was compared to a group of patients in whom dose adjustments were based on clinical symptoms. Full results of this study will be presented at future meetings.

While many questions remain regarding the utility of anti-TNF monitoring, I believe antibody testing will become part of mainstream clinical practice in the near future. Previously, clinicians did not really know why some patients failed anti-TNF therapy, but antibody testing now allows us to better understand what is happening in these cases. Patients who could potentially benefit from anti-TNF monitoring can be divided into 2 groups. One group consists of patients in whom anti-TNF therapy has been initiated but has not proven effective. In these patients, clinicians have to decide whether to dose escalate, switch to another anti-TNF drug, or abandon anti-TNF therapy. I think the data summarized in this supplement support the use of antidrug antibody testing in this setting, and I routinely perform such testing in my practice. The other group of patients in whom testing might be considered are those patients who are on anti-TNF therapy and are doing well. I am not yet persuaded that the available data are sufficient to support anti-TNF monitoring in this group; currently, I do not measure antibody levels or adjust drug levels in patients who are doing well. However, I remain open to the idea that the role of anti-TNF monitoring in clinical practice could change quickly. Indeed, clinicians will likely measure drug levels and/or antibody levels routinely in most or all patients in the coming months and years.

References

1. Reinisch W, Feagan BG, Rutgeerts PJ, et al. Infliximab concentration and clinical outcome in patients with ulcerative colitis. Presented at Digestive Disease Week; May 19–22, 2012; San Diego, California. Abstract 566.
2. Feagan BG, Singh S, Lockton S, et al. Novel infliximab (IFX) and antibody-to-infliximab (ATI) assays are predictive of disease activity in patients with Crohn's disease (CD). Presented at Digestive Disease Week; May 19–22, 2012; San Diego, California. Abstract 565.
3. Casteele NV, Cuypers L, Singh S, et al. Antibodies to infliximab can either be persistent or transient: a retrospective case-control study in IBD patients treated with infliximab maintenance therapy. Presented at Digestive Disease Week; May 19–22, 2012; San Diego, California. Abstract 563.
4. Casteele NV, Compernolle G, Ballet V, et al. Results on the optimisation phase of the prospective controlled Trough Level Adapted Infliximab Treatment (TAXIT) trial. Presented at Digestive Disease Week; May 19–22, 2012; San Diego, California. Abstract 1159.


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