A SPECIAL MEETING REVIEW EDITION

Serologic Monitoring and Testing in IBD: Highlights From the 2015 DDW and Best Use in Clinical Practice

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Special Reporting on:

- Dose Optimization of Infliximab Using Therapeutic Drug Monitoring Is More Effective Than Dose Optimization Based on Clinical Assessment Alone in Patients With Active Inflammatory Bowel Disease
- Thiopurine Metabolite Testing to Guide Management in Inflammatory Bowel Disease (IBD) Yields Clinical Benefit at 12 Months: A Retrospective Observational Study
- Higher Adalimumab Drug Levels Are Associated With Clinical and Endoscopic Remission in Patients With Crohn's Disease
- Adequate Trough Concentrations and Sustained TNF Suppression Early On During Induction Therapy With Adalimumab Predict Remission in Anti-TNF Naïve Crohn's Disease Patients

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Serologic Monitoring and Testing in IBD: Highlights From the 2015 DDW and Best Use in Clinical Practice

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Several studies presented at the 2015 Digestive Disease Week (DDW) evaluated the use of serologic monitoring and testing in patients with inflammatory bowel disease (IBD). These studies confirmed findings from previous research while providing new insights into the management of IBD.

Therapeutic Drug Monitoring of Anti-TNFα Agents

Previous data have shown that adjusting the dosage of anti–tumor necrosis factor-α (TNFα) agents based on therapeutic drug testing improved outcomes and was more cost-effective compared with dose adjustments based on empiric evidence.[1,2] In addition, therapeutic drug monitoring allows identification of patients with antibodies to infliximab, who should be switched to a different biologic agent (usually from the same class if the patient had an initial response), possibly with an immunomodulator. A study presented at the 2015 DDW by Orlaith Kelly, MBBCh, PhD, corroborated these findings, showing that dosage adjustments based on therapeutic drug monitoring resulted in fewer hospitalizations and fewer flares than adjustments based on clinical assessment.[3]

Therapeutic drug monitoring can identify patients with very low and mid-range levels of infliximab and can show the level of infliximab that an individual patient requires for a good outcome. It is equally important when therapeutic drug monitoring identifies high levels of infliximab in a patient who is not responding and continues to have inflammation—suggesting that the patient may require a drug with a different mechanism of action. It therefore makes sense to perform therapeutic drug monitoring because it provides useful data for patient management.

Previous studies have indicated that levels of anti-TNFα agents correspond to important outcomes.[4,5] A study by Eran Zittan, MD, and colleagues corroborated these earlier data by showing that levels of anti-TNFα agents correspond to mucosal healing.[6] It is becoming evident that mucosal healing may require higher levels of the anti-TNFα agent. Although earlier data had established that adalimumab levels of 5 μg/mL or higher were associated with normal C-reactive protein (CRP) activity,[7,8] this study showed that levels of more than 12 μg/mL were required to achieve both clinical and endoscopic remission.[6] In my experience, higher levels of an anti-TNF agent generally improve outcomes, especially mucosal healing, which represents the highest therapeutic goal. Although this study measured adalimumab, the findings are likely applicable to infliximab as well, although the drug levels will likely be different.

A study by Niels Vande Casteele, PharmD, PhD, and colleagues aimed to determine whether measurement of adalimumab levels could help identify which patients will respond to treatment.[9] The study assessed early time points during treatment with adalimumab among Crohn's disease patients who had not received prior anti-TNFα therapy. The study found that patients with higher levels of adalimumab even as early as week 4 were more likely to achieve clinical remission at week 12. Studies such as this one can be difficult to interpret because of uncertainties regarding cause and effect. Patients with higher levels of adalimumab may have had lower levels of TNFα and lower inflammatory burden that could be more easily neutralized by treatment. On the other hand, it is harder to achieve higher serum levels of the anti-TNF in patients who have a very high inflammatory burden and very high levels of TNF in the tissue. As a corollary to this, it is likely that mid-range levels of the anti-TNF are sufficient to suppress inflammation once mucosal healing has been achieved and patients are in the maintenance phase.

Another important point raised by this study was that some patients developed antibodies to adalimumab very early in treatment. It can be helpful to identify these patients. The results of this study strongly support early measurement of anti-TNFα concentrations, which can help determine

whether a patient requires dose escalation or a different type of therapy.

The study also found that clinical remission was more closely associated with trough concentrations rather than peak concentrations. This finding is important because the best time to measure adalimumab concentrations is still undecided. Although it had been thought that levels remain stable throughout the 2-week period between doses, there appears to be some variation.

My most recent approach to monitoring for anti-TNFα and antibodies is to test immediately after induction and before initiation of maintenance dosing. It is the early nadir in anti-TNFα levels that results in the development of antidrug antibodies. As shown by Vande Casteele and colleagues, early testing can also identify true nonresponders (who have high drug levels but active disease).[9] When only testing "reactively," there is the risk that the patient has already developed antibodies.

Thiopurine Metabolite Testing

Thiopurines, such as azathioprine and 6-mercaptopurine (6-MP), are clinically effective and cost-effective therapies for IBD. Studies in IBD have shown that levels of the thioguanine metabolite correlate with efficacy.[10,11] Although in the past, thiopurines had been used as monotherapy, the more recent approach is to use the thiopurine as a foundational drug when administering biologic therapy. Current biologic therapy for IBD consists of monoclonal antibodies, which have several limitations, including variable metabolism and clearance based on patient-specific factors and immunogenicity leading to the development of antidrug antibodies.[12,13] These antibodies against the drugs themselves can shorten their half-life. Thiopurines have been shown to decrease clearance of the anti-TNFs, leading to higher trough levels. The thiopurines are also associated with lower rates of antibodies against the anti-TNFs, but

it is not clear if this effect is caused by the immunosuppressive effects of the drugs or rather occurs because the anti-TNF levels remain higher.

Previous research has shown that thiopurine metabolite testing can be useful in IBD.[14,15] Patients who produce high levels of 6-methylmercaptopurine (ie, those with high thiopurine methyltransferase activity) are unable to generate sufficient 6-thioguanine nucleotide to achieve efficacy. In a study presented by Soong-Yuan Ooi, MBBS, thiopurine metabolite testing was used to identify the significant number of IBD patients (15%) in whom 6-MP and azathioprine predominantly produce the non-effective metabolite, namely 6-methylmercaptopurine, rather than the beneficial metabolite, 6-thioguanine, downstream of the drug.[16] Subsequent treatment of these patients with allopurinol improved efficacy, which has also been shown previously. The addition of allopurinol to azathioprine or 6-MP causes a dramatic shift to pure 6-thioguanine nucleotide production that can lead to improved clinical outcomes in this group of patients. However, this drug combination must be carefully monitored so as not to induce bone marrow suppression caused by extremely high levels of 6-thioguanine.[17] To achieve this effect, the dose of azathioprine can often be less than 50 mg when combined with allopurinol. In other situations, if the goal is simply to raise levels of the biologic through the use of combination therapy with thiopurine, then levels of 6-thioguanine nucleotide above 125 pmol/8×10^8 red blood cells appear to be sufficient.[18]

With these studies and others, this year's DDW has provided data that may assist physicians in fine-tuning the art of administering biologic and combination therapy in IBD.

Disclosure

Dr Abreu is a member of the Scientific Advisory Boards of AbbVie Laboratories, Shire Pharmaceuticals, Asana Medical, and Celgene. She has performed consult-

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Dose Optimization of Infliximab Using Therapeutic Drug Monitoring Is More Effective Than Dose Optimization Based on Clinical Assessment Alone in Patients With Active Inflammatory Bowel Disease

O.B. Kelly, S. O'Donnell, J.M. Stempak, A.H. Steinhart, M.S. Silverberg

In patients with an initial response to anti–tumor necrosis factor-α (TNFα) therapy, the recurrence of clinical symptoms can provide the impetus for empiric dose adjustments. Alternatively, therapeutic drug monitoring to assess both drug and anti-drug antibody levels could provide a rational approach to optimizing dose adjustments to achieve maximum clinical benefit. At the 2015 DDW, Orlaith Kelly, MBBCh, PhD, of the Mount Sinai Hospital in Toronto, Ontario presented results of a retrospective study that examined differences in outcomes in IBD patients when doses of infliximab were adjusted based on clinical factors vs therapeutic drug monitoring.[1]

All patients had a primary response to infliximab and underwent dose intensification between 2008 and 2014. The therapeutic drug monitoring cohort included 88 patients (with 136 dose adjustments), and the clinical factors cohort included 136 patients (with 155 dose adjustments). In both cohorts, patients had received infliximab for a median of 45 months. The median time from first infusion to first dose adjustment was 15 months. Patients in the therapeutic drug monitoring cohort had a higher median baseline level of C-reactive protein (23 ± 2 g/L vs 11 ± 3 g/L; *P*=.01). After the dose adjustment, the therapeutic drug monitoring arm had a greater proportion of patients with endoscopic remission (66.2% vs 47.4%; *P*=.03; Figure 1) and clinical response (69% vs 57%; *P*=.007), with fewer mean hospitalizations (0.3 vs 0.71; *P*=.03) and flares (15 vs 23; *P*=.02). In the cohort of patients who underwent therapeutic drug monitoring, dose adjustment significantly improved the median trough level of infliximab from less than 1 μg/mL to 12.5 μg/mL (*P*<.001). After dose adjustment in the clinical factors cohort, the median trough level was 6.5 μg/mL, a significant difference from the monitoring cohort (*P*<.01). Serum levels of albumin and C-reactive protein were associated with a clinical response (*P*=.02 and *P*=.03, respectively).

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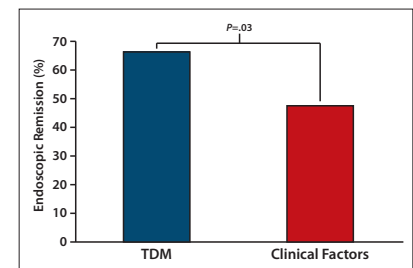
Figure 1. In a retrospective trial of inflammatory bowel disease patients receiving infliximab, endoscopic remission was significantly greater when the infliximab dose was adjusted based on therapeutic drug monitoring (TDM) vs clinical factors alone. Adapted from Kelly OB et al. Dose optimization of infliximab using therapeutic drug monitoring is more effective than dose optimization based on clinical assessment alone in patients with active inflammatory bowel disease [DDW abstract Tu1316]. *Gastroenterology*. 2015;148(suppl 1):S857.[1]

Thiopurine Metabolite Testing to Guide Management in Inflammatory Bowel Disease (IBD) Yields Clinical Benefit at 12 Months: A Retrospective Observational Study

S.J. Ooi, M. Gounder, R. Grafton, P. Leach, P.A. Bampton, A. Sechi, W.S.W. Ng, S.J. Connor, J.M. Andrews

For IBD patients receiving treatment with the thiopurines, azathioprine or 6-mercaptopurine, dose optimization is desirable not only to achieve a clinical response but also to diminish the potential for bone marrow suppression and for hepatotoxicity that is sometimes associated with thiopurine metabolites. Therapeutic drug monitoring consists of measuring serum levels of the thiopurine metabolites, 6-thioguanine nucleotides (6-TGN) and 6-methylmercaptopurine (6-MMP). At the 2015 DDW, Soong-Yuan Ooi, MBBS, of the Liverpool Hospital in Liverpool BC, New South Wales, Australia presented results of a study that evaluated outcomes in IBD patients in whom thiopurine dose adjustments were based on metabolite levels and who were followed for at least 12 months after the initial dose adjustment.[1]

This retrospective study included adults with IBD (n=343, 72% Crohn's disease) who had been treated with azathioprine or 6-mercaptopurine for at least 4 weeks prior to the initiation of therapeutic dose monitoring. The therapeutic range of 6-TGN was defined as 235-450 pmol/8×10^8 red blood cells. The median age was 41 years, 52% of patients were male, and 64% had active disease at baseline. Reasons for use of therapeutic dose monitoring included proactive dose assessment (48%), symptom flare (23%), ongoing active disease (21%), and adverse drug reaction (7%). Based on therapeutic dose monitoring, continuation of thiopurine therapy was maintained in 84% of patients, while 8% went on to receive anti-TNFα therapy, 4% went on to receive another medical agent, and 1% of patients had surgery.

At 12 months, 72% of patients were in clinical remission (compared to only 36% at baseline), 19% had active disease, 6% showed clinical improvement in disease activity, and 3% had unknown status (Figure 1). In total, 267 patients were in clinical remission or improvement at 12 months, and for over half of these patients, this outcome was attributed to thiopurines, either alone (43%) or combined with allopurinol (15%). The remaining patients required anti-TNFα therapy (23%), surgery (9%), and other treatments (4%). Based on univariate logistic regression analysis, the only predictor of 12-month clinical remission or improvement among patients receiving thiopurine therapy was the presence of remission at baseline (OR, 2.87; 95% CI, 1.20-6.89; P=.02).

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Figure 1. Disease activity among inflammatory bowel disease patients on thiopurines at baseline and 12 months after dosing based on metabolite measurements. Adapted from Ooi SJ et al. Thiopurine metabolite testing to guide management in inflammatory bowel disease (IBD) yields clinical benefit at 12 months: a retrospective observational study [DDW abstract Tu1330]. *Gastroenterology*. 2015;148(suppl 1):S861.[1]
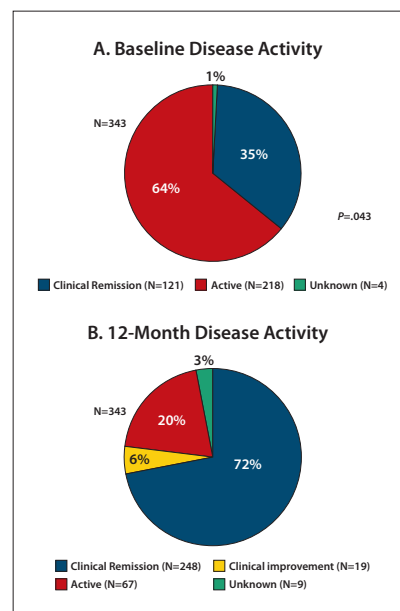
Higher Adalimumab Drug Levels Are Associated With Clinical and Endoscopic Remission in Patients With Crohn's Disease

E. Zittan, B. Kabakchiev, J.M. Stempak, G.C. Nguyen, K. Croitoru, G.A. Van Assche, A.H. Steinhart, M.S. Silverberg

The loss of response to anti-TNFα therapy can result from low serum drug concentrations or the presence of antibodies that neutralize drug activity. At the 2015 DDW, Eran Zittan, MD, of the Mount Sinai Hospital in Toronto, Ontario presented results of a study that examined whether adalimumab drug levels and antibodies to adalimumab were associated with clinical and/or endoscopic remission in patients with Crohn's disease.[1]

The study enrolled Crohn's disease patients treated with adalimumab between 2005 and 2013. Clinical remission was defined by a Harvey-Bradshaw Index score of 4 or less. Endoscopic remission was defined by the absence of ulceration in all ileocolonic segments. The 88 patients had a median age of 31 years, a median disease duration of 11.5 years,

and a mean time on adalimumab of approximately 2.5 years. Fifteen patients (16%) had elevated antibodies to adalimumab titers (≥1 U/mL). Median serum adalimumab levels were significantly higher in patients with low serum antibodies (12.7 μg/mL vs 1.9 μg/mL; $P<.000001$). Drug concentrations were also higher in patients with normal C-reactive protein levels vs those with elevated levels (13.4 μg/mL vs 7.9 μg/mL; $P<.01$). Patients with mucosal healing had a significantly higher median level of serum adalimumab vs the patients without mucosal healing (17.4 μg/mL vs 6.6 μg/mL; $P<.00001$; Figure 1). The median level of serum adalimumab was also significantly higher in patients who exhibited both clinical and endoscopic remission compared with those who did not (12.8 μg/mL vs 7.1 μg/mL; $P<.04$).
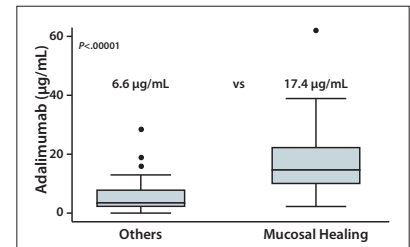

Figure 1. Crohn's disease patients with mucosal healing had a significantly higher median level of serum adalimumab vs those without mucosal healing. Adapted from Zittan E et al. Higher adalimumab drug levels are associated with clinical and endoscopic remission in patients with Crohn's disease [DDW abstract Tu1299]. *Gastroenterology.* 2015;148(suppl 1):S852.[1]

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Adequate Trough Concentrations and Sustained TNF Suppression Early On During Induction Therapy With Adalimumab Predict Remission in Anti-TNF Naïve Crohn's Disease Patients

N. Vande Casteele, D.R. Mould, A. Gils, S. Tops, K. Van den Broeck, V. Ballet, M. Ferrante, G.A. Van Assche, S. Vermeire, F.J. Baert

Serum levels of anti-TNFα agents may correlate with the likelihood of remission in Crohn's disease patients. At the 2015 DDW, Niels Vande Casteele, PharmD, PhD,

of the Laboratory for Therapeutic and Diagnostic Antibodies, KU Leuven, Leuven, Belgium presented results from a prospective, open-label study investigating the correlation between

serum adalimumab concentrations and objective markers of inflammation and disease activity.[1] The study enrolled 23 patients with moderate-to-severe Crohn's disease who had not received

a prior anti-TNFα agent. Serum samples were collected at weeks 0, 1, 2, 3, 4, and 12. Outcomes were measured after 12 weeks of treatment with adalimumab. Clinical remission was defined as a Harvey-Bradshaw Index score of 4 or less.

At week 12, 70% of patients had achieved a clinical remission. The baseline serum concentrations of C-reactive protein and TNF were similar between patients who achieved remission and those who did not (P=.504). Patients who achieved remission had a significant decrease in median C-reactive protein (P<.01) and a sustained reduction in serum TNF concentration (P<.01) from baseline to 12 weeks. These values did not decrease significantly among patients who did not achieve remission (P=.051 and P=.153, respectively). Drug exposure, defined by the area under the curve of adalimumab concentration during weeks 0 to 4, was significantly greater for patients who achieved remission vs those who did not (P=.043; Figure 1). Clinical remission at week 12 corresponded more strongly to the trough concentrations than the peak concentrations. Based on receiver operating characteristic analysis, clinical remission at week 12 was associated with serum adalimumab concentrations above 9.7 μg/mL at week 2 and above 11.0 μg/mL at week 4, with 100% specificity and 69% sensitivity for both concentrations. One patient who did not achieve remission was a primary nonresponder, and 1 patient who achieved remission developed antibodies to adalimumab detected at week 12.

Reference

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Figure 1. In a study of patients with Crohn's disease, drug exposure (measured as the area under the adalimumab concentration curve) was significantly greater for patients who achieved remission (remitters) vs those who did not (nonremitters). Adapted from Vande Casteele N et al. Adequate trough concentrations and sustained TNF suppression early on during induction therapy with adalimumab predict remission in anti-TNF naïve Crohn's disease patients [DDW abstract Tu1308]. *Gastroenterology*. 2015;148(suppl 1):S854-S855.[1]
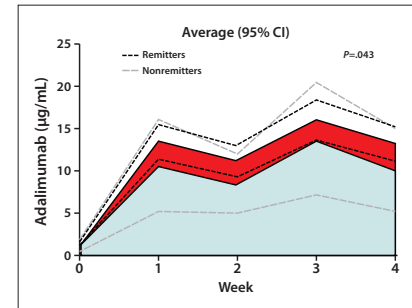
CASE STUDIES

Use of Blood Testing to Assist in Both Diagnosis and Therapy Management for an Adolescent IBD Patient

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The patient initially presented at age 10 after experiencing 6 weeks of bloody stools, diarrhea, and weight loss. He underwent esophagogastroduodenoscopy/colonoscopy, which showed gastritis, mild duodenitis, pancolitis, and a normal terminal ileum with no granulomas. He was diagnosed with indeterminate colitis. He began treatment with a mesalamine. He developed pericarditis, which was treated with prednisone.

The mesalamine was discontinued, given its association with pericarditis. Once the thiopurine methyltransferase (TPMT) genotype was confirmed as normal, then treatment was initiated with 6-mercaptopurine (6-MP). Shortly afterward, a liver function test showed elevated levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Thiopurine metabolite testing demonstrated a 6-methylmercaptopurine level of 5761 pmol/8 × 10^8 red blood cells and a 6-thioguanine level of 152 pmol/8 × 10^8 red blood cells. Based on these laboratory results, along with increasing arthralgia, 6-mercaptopurine was discontinued and adalimumab was initiated. The patient tolerated this treatment well, with a good response. His serum inflammatory markers and transaminases normalized. For the next several years, he experienced good weight gain and linear growth.

The patient, now age 16 years, recently presented for routine follow-up. He was still receiving treatment with adalimumab. His erythrocyte sedimentation rate was noted to be slightly elevated as compared with his previous visit. Clinically, he felt well, with no diarrhea or hematochezia. He was of normal weight. He had been following a more healthy diet and reported a weight loss of 20 pounds, which was more than he and his mother had expected. This weight loss raised concern regarding active disease. Therefore, a stool calprotectin test was ordered, and levels were elevated at 541 μg/g. (The normal level is <163 μg/g.)

His unexplained weight loss and elevated calprotectin, without bloody stool, raised suspicion that the patient might have Crohn's disease with small bowel involvement. His mother was concerned because the patient's aunt has Crohn's disease and has undergone multiple surgeries. We ordered an IBD sgi Diagnostic test, which showed markers that were positive for Crohn's disease and that excluded indeterminate colitis. Further evaluation of the small bowel, with a patency capsule and then capsule endoscopy, revealed diffuse aphthous lesions throughout, consistent with Crohn's disease (Figure 1).

The patient's active disease led to concern for a secondary nonresponse to adalimumab, and thus an Anser
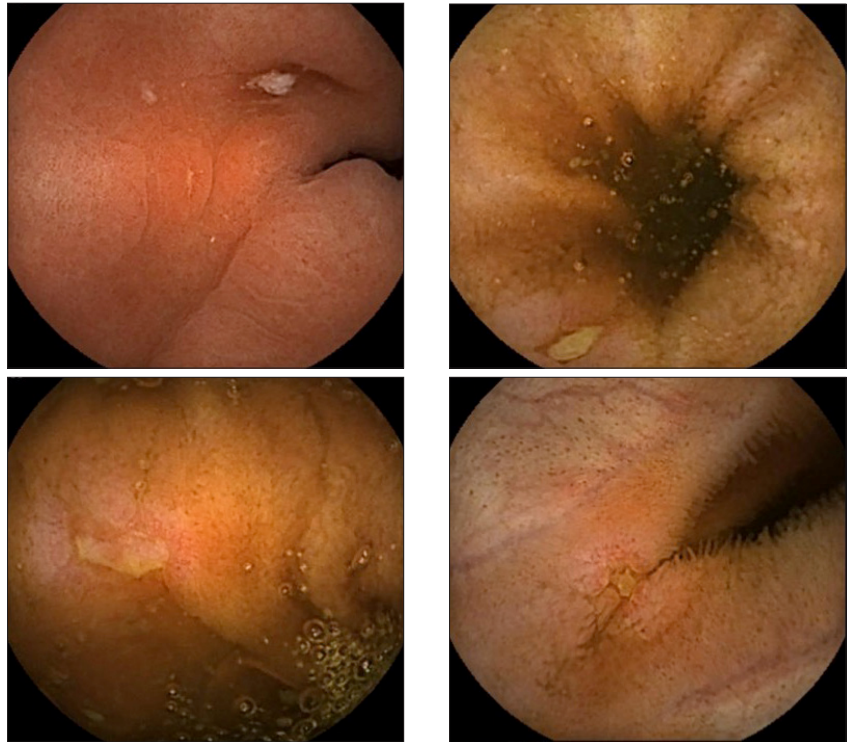

Figure 1. These images from wireless capsule endoscopy reveal small bowel ulcerations and erosions in the proximal, mid, and distal small bowel.

ADA test was administered. The Anser ADA test showed that the patient had developed antibodies to adalimumab, with an adalimumab concentration of less than 1.6 μg/mL and an antibody level of 14.7 U/mL. The patient will now be switched from adalimumab to infliximab because his initial success with adalimumab indicates that he is responsive to the anti-TNF mechanism of action. After the risks and benefits were discussed with the patient and his family, we decided to initiate low-dose oral methotrexate to avoid immunogenicity. At week 14, an infliximab trough concentration will be obtained and dose adjustments made, if necessary, to ensure a therapeutic trough level.

A Woman With Crohn's Disease Who Develops Symptoms During Treatment With 6-MP

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The patient is a 34-year-old woman with Crohn's ileitis and right-sided colitis. She had developed several flares, which were treated with corticosteroids. After her thiopurine methyltransferase (TPMT) phenotype was found to be normal, she began treatment with 6-mercaptopurine (6-MP; 1 mg/kg) and did well. She was able to taper off budesonide and maintain remission.

When she presented to me, she was clinically in remission, but she had evidence of erosions in the ileum (Figure 1), cecum, and ascending colon; some granularity; and edema. Her C-reactive protein (CRP) level was slightly elevated at 15 mg/L. (The normal level is 0-4 mg/L.) Her dosage of 6-MP was 75 mg/day (approximately 1 mg/kg). We tested her 6-MP metabolites. The thioguanine nucleotide (6-TGN) was 250 pmol/8×10^8 red blood cells, and the 6-methylmercaptopurine (6-MMP) was 1100 pmol/8×10^8 red blood cells. We discussed goals of care, including the additional potential benefits of endoscopic remission, and mentioned that endoscopic healing might be achieved with anti-TNF therapy. At that time, the patient declined to initiate this treatment.

She presented for follow-up several months later. She had started to experience some symptoms, albeit relatively mild ones. A magnetic resonance enterography showed approximately

Figure 1. The terminal ileum, as shown during the first colonoscopy.

25 cm of mildly to moderately active disease. Based on this evidence of disease, as well as her symptoms, we performed another colonoscopy (Figures 2 and 3). The disease appeared to have progressed. At that point, she opted for anti-TNF therapy. She began treatment with infliximab and did well. Her symptoms improved.

At week 14, we checked her infliximab trough concentration, and it was 10 µg/mL, with no detectable antibodies to infliximab. The CRP level normalized. We are currently continuing treatment with 6-MP and infliximab. The goal in the near future is to repeat the colonoscopy and assess for mucosal healing. If the mucosa is healed, and if a repeat infliximab trough concentration during the maintenance phase shows adequate levels, then we will discontinue treatment with 6-MP. After stopping 6-MP, we
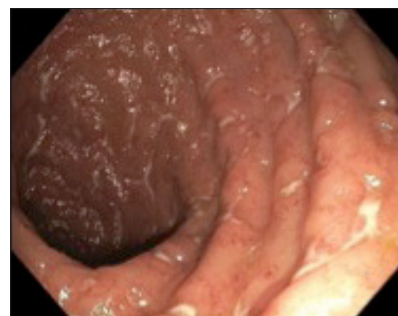

Figure 2. The terminal ileum, as shown during the second colonoscopy.

Figure 3. The cecum, as shown during the second colonoscopy.

would repeat testing of the trough infliximab concentration to ensure that it remains higher than 5 µg/mL. The plan would be to continue to utilize optimized monotherapy with infliximab based on proactive monitoring of infliximab trough concentrations.

Disclosure
Dr Cheifetz has consulted for Janssen, AbbVie, UCB, Takeda, and Prometheus.

A Young Woman With Crohn's Disease and Low Infliximab Levels Due to Anti-Infliximab Antibodies

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The patient is a 26-year-old woman who has small-bowel ileal Crohn's disease. She was diagnosed at age 19 years, when she presented with an ileal stricture. At that time, she underwent an ileal resection. Postoperatively, she did well. Six months after surgery, a colonoscopy showed disease in the terminal ileum classified as Rutgeerts score i2 (>5 aphthous lesions with normal mucosa between the lesions or skip areas of larger lesions or lesions confined to the ileocolonic anastomosis). Clinically, she was asymptomatic. The patient's C-reactive protein (CRP) level was slightly elevated, at 4.1 mg/L. The thiopurine methyltransferase (TPMT) enzyme activity level was 18.4 U/mL (within the normal range). She began treatment with 6-mercaptopurine (6-MP), at 100 mg/day. She developed transaminitis, with an aspartate aminotransferase (AST) of 110 U/L and an alanine aminotransferase (ALT) of 88 U/L. Testing for thiopurine showed a thioguanine nucleotide (6-TGN) metabolite level of 225 pmol/8 × 10^8 red blood cells and a 6-methylmercaptopurine (6-MMP) level of 5955 pmol/8 × 10^8 red blood cells. Studies have indicated that levels of 6-MMP higher than 5700 pmol/8 × 10^8 red blood cells may be associated with hepatotoxicity.

Based on the patient's risk of recurrent disease, as well as her elevated CRP, we initiated combination therapy with adalimumab plus low-dose 6-MP (25 mg/day). She did well on this regimen for 9 months. She then began to experience recurrent pain in the right lower quadrant. Colonoscopy revealed active inflammation of the terminal ileum and Rutgeerts score i2 disease. An antibody test showed that she had developed antibodies to adalimumab, at a level exceeding 100 U/mL. We therefore switched treatment to infliximab with methotrexate. After a year of this regimen, she underwent a colonoscopy, which showed mucosal healing with no ulcerations in the terminal ileum. She received this combination for an additional year and continued to do well.

Insurance changes compelled the patient to discontinue treatment with infliximab and methotrexate and to end follow-up visits. She returned to our office 1.5 years later with right lower quadrant pain. Her hemoglobin had dropped to 10 g/dL. Her CRP was 8 mg/L. (The normal range is 0 to 4 mg/L.) Her sedimentation rate was elevated, at 35 mm/hour.

A colonoscopy showed ileal narrowing, which prevented passage of a pediatric colonoscope. Magnetic resonance enterography showed acute and chronic inflammation, but no prestenotic dilatation of the terminal ileum. The patient did not have any signs of obstruction. She received a course of budesonide. Afterward, we discussed restarting infliximab vs trying certolizumab, another monoclonal antibody to tumor necrosis factor–α. We selected certolizumab. The patient did not tolerate this treatment well. She experienced severe fatigue and other adverse events.

We stopped treatment with certolizumab and discussed other options. After our discussion, the patient elected to retry infliximab because she had felt the best while receiving this therapy. Also, vedolizumab was not available at that time. The patient was aware of the risk that she might have antibodies to infliximab due to the drug holiday. We decided to administer an infusion of infliximab.

Ten days later, we checked the patient's antibody levels and drug levels. The drug level was 0 μg/mL, and the antibody level was more than 100 U/mL. Knowing that the patient's drug level was 0 μg/mL allowed us to avoid a second dose of infliximab, which would have caused an infusion reaction. We are now in discussion with the patient about other therapeutic options, including a clinical trial or vedolizumab.

Disclosure
Dr Parekh has no real or apparent conflicts of interest to report.