New Directions on Therapeutic Drug Monitoring in IBD

Announcer:
This is CME on ReachMD. This activity titled: New Directions on Therapeutic Drug Monitoring in IBD, is jointly provided by Postgraduate Institute for Medicine and Medtelligence, and supported by an independent educational grant from Quest Diagnostics.

Prior to beginning this activity, please be sure to review the faculty and commercial support disclosure statement, as well as the learning objectives.
Here’s your faculty, Dr. Alan Moss and Dr. Adam Cheifitz.

Dr. Moss:
Hi, I’m Allen Moss. I’m an Associate Professor of Medicine at Harvard Medical School and Director of Translational Research at the IBD Center at Beth Israel Deaconess Medical Center in Boston.

Dr. Cheifetz:
And I’m Adam Cheifetz, Associate Professor of Medicine at Harvard Medical School and Director of the
Center for Inflammatory Bowel Disease at Beth Israel Deaconess Medical Center in Boston, Massachusetts.

Today we'll be discussing issues related to the effectiveness of TNF inhibitors for inflammatory bowel disease as well as the role of therapeutic drug monitoring. We will then review cases that demonstrate how information from recent studies can be used in your clinical practice.

So, Dr. Moss, why don't you start us off? What are the challenges of optimizing treatment with anti-TNF inhibitors in inflammatory bowel disease?

Dr. Moss:
Thanks, Adam. So, the biologic class of medications have been a major development in the treatment of inflammatory bowel disease over the last 20 years, and unlike small molecules, all these biologics are monoclonal antibodies and, therefore, as foreign proteins are potentially immunogenic in the recipients. If we think about the structure of these, they are either a full monoclonal antibody, such as infliximab or adalimumab, or they are a component of an antibody, such as certolizumab. Regardless of their composition, they are all able to induce an immune response from patients that can disrupt the ability of these drugs to treat their inflammatory bowel disease.

If you look at the data from clinical trials that led to the approval of this class of drugs and follow patients over 18 to 24 months during maintenance trials, a key feature has been that many, and many cases up to 40% to 60% of patients over time, eventually lose their remission or relapse despite being on this class of drugs, and this is the same whether you're looking at infliximab trials or adalimumab trials or certolizumab trials. And even in clinical practice, what has been noted is that what we typically see is, over time, many patients who are able to get into remission with anti-TNFs do not maintain that remission over time. A very nice study from Europe showed many years ago that really after about 2 years or so, about half the patients are no longer in remission despite ongoing therapy with adalimumab.

Now, why is this? Well, there are many reasons for patients developing symptoms while on these class of drugs. What we do know from large studies of cohorts in certain centers, that typically, about 20% to 25% of these patients the problem is immunogenicity. They have either developed antibodies against the anti-TNF and have low drug levels or have low drug levels even in the absence of anti-drug antibodies. And so this remains something that potentially we could address in practice in how we use these drugs and how we monitor patients.

The reason anti-drug antibodies, or ADAs, are important, is that we know from pharmacokinetic studies that patients who have antibodies in circulation against these drugs typically have a much more rapid
decline in drug levels over time. The slide that we’re showing here looks at infliximab, and what it highlights is that in patients who have infliximab antibodies, their levels drop very rapidly over time and often are between infusions. In contrast, patients who have no antibodies generally maintain their levels in a much higher range over time.

Now, if you think about the clinical impact of this, what we know from many studies is that patients generally who have no anti-drug antibodies, in this case to infliximab, are more likely to remain in remission over time in comparison to patients who develop anti-drug antibodies who often will lose response over time, and this has been shown both in clinical trials and in many clinical observational studies. So that focuses on antibodies.

The other issue we talked about is just having low drug levels per se, even with or without antibodies. And we know from studies both in colitis and in Crohn’s disease that patients who maintain their drug levels above a certain range are more likely to either obtain remission or maintain remission over time than patients who have levels below a certain range. One example is a paper from Seow, et al, that we’re illustrating on the slides showing that only 15% of patients who had levels below 1.96 of infliximab were in remission versus almost 70% of patients who had levels above 1.96.

Now, we looked many years ago at a number of different trials, and you can see that, in general, patients who lose response to the drug generally have lower levels than patients who maintain remission, and this is across many different patient cohorts and both in ulcerative colitis and in Crohn’s disease.

So, this raises a number of questions, and we’re looking forward to hearing Dr. Cheifetz discuss this. Firstly, in our patients who have active disease or on patient’s remission, should be routinely measuring drug levels and measuring anti-drug antibody levels in their blood. Secondly, when we do measure them, how to interpret what’s an appropriate level of drug and what’s a level of antibody we should take action to. And then finally, and this is the more recent topic, is, what’s the role of routinely measuring levels in all patients regardless of whether they are in remission or not? And this is the so-called proactive testing strategy.

Dr. Cheifetz:
Excellent, Alan. Thank you very much for that great introduction to the topic. I will take the group through the role of therapeutic drug concentration monitoring, particularly with anti-TNF therapies, really focus on the difference between reactive and proactive therapeutic drug monitoring, and I hope to really show the potential benefits for proactive TDM.

So, starting with reactive drug concentration monitoring, really the definition is measurement of serum
trough concentrations and antibody levels in the setting of primary, or more commonly secondary loss of response to a biologic agent, and the reason for this is to really see how much drug is on board and if there are antibodies and what level they are to better inform whether you’re going to give more of the drug, potentially add an immunomodulator, switch within class, in this case anti-TNF therapy, or switch out of class.

And there have been several guidelines on therapeutic drug monitoring or consensus statements that all are in favor of reactive therapeutic drug monitoring, particularly in those patients who are losing response or having a secondary loss of response, both from the AGA as well as ECCO, and the Australian TDM Consensus as well.

This really all came about... Probably the first study and still one I like to show is a study from Afif and the group at Mayo Clinic where they looked at about with 150 patients who had infliximab concentration and antibodies measured, and really they found that the test result impacted care in 73% of these patients. Now, most of these patients had these levels checked for secondary loss of response, and what I really find important and important to point out is, in those patients that had therapeutic infliximab drug concentrations, there was no evidence of active inflammation in the majority of those patients. In 62% of those patients, there was no evidence of inflammation, meaning any change to the infliximab would not have been the right decision. These are patients who have symptoms of what was thought to be active IBD but in fact was unrelated possibly irritable bowel, bile salt malabsorption, some other reason for symptoms. And so the most important thing when assessing secondary loss of response is really having objective evidence that the patients have ongoing or active inflammatory bowel disease.

After that, it makes sense. Those patients with subtherapeutic infliximab concentrations that were dose escalated, almost 90% had a complete or partial response, which makes sense. If you don’t have enough drug on board, you give more drug, those patients do better. Interestingly, those patients who had subtherapeutic infliximab concentrations and switched anti-TNF, here you only gained response in a third of your patients. And again, this goes with previous trials, including the GAIN trial and other trials, which show if you’re failing 1 agent, and in this case because you’re clearing the drug quickly, you’re not going to respond as well to a second anti-TNF—in this case it was adalimumab—because, again, you’re potentially going to clear that quickly as well. Those patients that had antibody positive or ATI positivity and you switched anti-TNF, again you got 92% response. These patients responded to an anti-TNF. They stopped responding because of antibody development. So if you switch within class to another anti-TNF, you recapture response in the majority of patients.

Those patients that were antibody positive and were dose escalated, here you were only able to recapture just under 20% of those patients. I think it’s a little bit more subtle than just antibody positive
and antibody negative, as I think we should be trying to look at the titer of antibodies and if they are high titer antibodies versus low titer antibodies, although there’s definitely less data in this situation.

So this is a nice algorithm regarding reactive testing. So, if you have a secondary loss response, again the most important thing is to confirm objective evidence of active disease. Check drug concentration and antibodies. If there is a subtherapeutic concentration, as we said, and there are no antibodies, dose escalate. Again, it makes more sense to decrease the interval than it does necessarily to increase the dose. You get more bang for your buck as far as pharmacokinetics are concerned. If the antibodies are positive, and again, if they are high titer antibodies, you can switch to another anti-TNF if necessary. You can switch out of class. If they are low-level antibodies, my bias is to typically optimize the drug someone’s on, again by dose escalation, and there’s data for just adding on an immunomodulator. Always you could change to another anti-TNF, and even if necessary change outside, but again, if these patients responded to an anti-TNF, I typically like to stay within class.

If they have a therapeutic anti-TNF drug concentration, which I think is rare—that’s maybe 15% of your patients... It’s far more common to have secondary loss of response due to low drug concentration than it is to have therapeutic anti-TNF concentrations. In this case they have enough drug on board and yet they are still not responding, so for whatever reason their disease mechanism switched—so, whereas before they were a responder to anti-TNF, now they are not. This is where you are best off switching out of class to a different mechanism.

This reactive testing algorithm has been shown to be more cost-effective and better direct care than just empiric dose escalation. This is a study by Fernando Velayos where he modeled reactive testing versus empiric dose escalation, and although there were similar rates of remission and response between the 2 groups and similar quality adjusted life years, the reactive testing was less expensive, and importantly, it gave more drug to those who could use it, and patients were seen to have lower use of high-dose biologics and have a greater time off of biologics.

Now on to proactive drug concentration monitoring, which is where I personally think the field, hopefully, should be heading. Proactive TDM is measurement of trough concentration and antibodies with the goal of optimizing these concentrations to achieve a threshold concentration at specific time points, whether it’s during induction, at the end of induction, or during maintenance, and the goal here is really to attain adequate drug concentrations and thereby decrease the risk of antibody formation and improve outcomes, both hopefully in the short-term and the long-term.

This also has been looked at by several guidelines or consensus statements, not nearly as many as reactive TDM, but here there are 2 groups that were in favor of proactively checking drug concentrations and antibodies. Both the Australian group, which recommended it after induction in
patients in remission and periodically in patients in clinical remission, as well as the BRIDGE group found it appropriate at least once during the first year of maintenance therapy to check drug concentrations. The AGA felt that there wasn’t enough evidence yet, and they felt that the role of proactive TDM was uncertain.

So, again, Alan touched on this, and I’ll just show it again. Again, this is studies with infliximab and adalimumab both in Crohn’s and ulcerative colitis, really just to point out, as Alan mentioned, higher drug concentrations are associated with better outcomes. And interestingly, when you look at it, the higher the drug concentration, often times the more objective the clinical outcome. Here you can see clinical response, higher clinical remission and even normalization of fecal calprotectin and C-reactive protein, higher than that mucosal healing, and maybe the toughest endpoint is fistula healing. What’s also been shown, as Alan mentioned, is that low drug concentrations, typically less than 3.5 or 3, are associated with antibody formation and treatment failure.

There is a number of factors that play into how quickly people clear these monoclonal antibodies. As you can see here, only 1, the concomitant use of an immunomodulator, actually decreases drug clearance, increases the concentration of the monoclonal antibody and improves outcomes. All the others, as Alan mentioned—presence of anti-drug antibodies and then the sicker the patient is, high baseline TNF, low albumin, high CRP—those all increase drug clearance, so typically, the sicker patient is, the more quickly they are going to clear the drug and the more drug they are going to need.

Therapeutic drug concentration monitoring is not novel. This is not new. We have been doing it for years, even in GI—the use of cyclosporin and tacrolimus in ulcerative colitis during residency, the use of vancomycin and gent- in sepsis. It’s this concept of a therapeutic window. In some drugs it’s high concentrations that above a certain level result in increased toxicity, and no matter what the drug, low concentrations or inadequate concentrations are just not effective. And again, with these monoclonal antibodies, these biologics, low concentrations are not only not effective, but they can lead to immunogenicity.

This is a nice prospective trial that was done in Belgium called the TAXIT trial where they basically enrolled patients on infliximab with IBD with a stable clinical response and dose optimized all patients, so every patient rolling into the study was optimized to a trough level of 3 to 7. Then, and only then, were they then randomized to infliximab dosing based on clinical symptoms and CRP, which is standard of care, or continued dosing to a therapeutic window, or so-called proactive TDM. And you can see here just a 1-time dose escalation in those Crohn’s patients who had less than 3 mcg/mL resulted in more patients being in remission on the left, and you can see on the right improvement in C-reactive protein. So again, just 1-time dose optimization in these patients resulted in better disease
control. Unfortunately, probably due to study design, the primary endpoint of remission at 1 year was no difference between the 2 groups. Again, I think that’s because all patients were initially optimized so everybody started from the same level. They were then only followed for a year. And I think the level of 3 to 7 may be on the lower end of where we want patients.

Despite that, several secondary endpoints favored dosing to an infliximab concentration or proactive TDM. Fewer patients needed rescue therapy. Fewer patients had undetectable trough concentrations. More patients were in that therapeutic window. And importantly, there was a similar cost between the 2 groups because 25% of patients underwent dose deescalation because their level was greater than 7 mcg/mL.

We published a study all the way back now in 2014 that compared a group of patients who were getting proactive therapeutic drug concentration monitoring to a window of 5 to 7—sorry, 5 to 10—and compared them to a control group from our center who were undergoing standard of care, which was either reactive therapeutic drug monitoring or just empiric dose escalation, and you can see there on the right in blue, the group that underwent proactive TDM had a much longer duration on infliximab than the group that was getting standard of care and more patients remained on drug.

More recently, in conjunction with a group from UPenn, we looked at 264 patients during the maintenance phase who underwent either proactive or reactive therapeutic drug monitoring, and we based this on what their first test was and compared the 2 groups, and here you can see there was less treatment failure and, importantly, less IBD-related surgery, antibody formation, IBD-related hospitalization, and not shown are serious infusion reactions in the group that was having proactive TDM compared to reactive TDM.

As important as it is—and where most of the data is, is in the maintenance phase—checking proactively is probably more important during the induction phase when these patients are sicker. As I mentioned, the patients that have high CRPs, low albumins, high TNF levels, is probably where they need more drug.

This was a nice study from Marla Dubinsky that showed that week 14 or post-induction levels of infliximab of greater than 7 actually correlated with week 52—sorry, week 54 outcomes and persistent remission. So, if you can get those patients controlled and have good drug concentrations after induction, odds are good these patients are going to do well in the long run.

One other concept is the use of proactive TDM and optimizing monotherapy in hopes of potentially avoiding combination therapy. We know, particularly based on the SONIC trial, that combination therapy with infliximab and azathioprine improves outcomes, particularly in those patients naive to
immunomodulators and biologics. However, we also know that combination therapy has been associated with a higher risk of adverse events, including opportunistic and serious infection, lymphoma, and even hepatosplenic T-cell lymphoma, however rare it is.

The hypothesis is that combination therapy with an immunomodulator increases the drug concentrations of the anti-TNF agent and decreases anti-drug antibodies, and the concept is if you can do this and dose appropriately from the beginning with just an anti-TNF therapy and proactive TDM, perhaps you can do it in lieu of using combination therapy, as combination therapy tends to be markedly underused.

This is a reanalysis of the SONIC trial where you can see it really looked like it was the trough concentration that was associated with the outcomes and not necessarily combination therapy. On the left you can see that combination therapy in blue really has more patients in the higher quartile. So those patients in quartile 4 with trough concentrations of greater than 5 was many more patients in combination therapy than in monotherapy, whereas group 1 with almost undetectable trough concentrations was mostly the group that was getting monotherapy. On the right, when you break it down into quartiles, you can see that it really was the amount of drug that was in the patient’s system, not necessarily where they were getting mono or combination therapy. You can see on the left I unfairly circled combination therapy with low drug concentrations and on the right monotherapy with high drug concentrations.

Despite the data I showed you—and this was just a quick run-through—there are a number of questions remaining, and Alan hinted at these. What are the right time points for proactive? Most of the data is with maintenance, although I think it’s even more important during induction and certainly by the end of induction. We can talk about is trough the most important endpoint, or perhaps, during induction, is area under the curve or the peak? What are the optimal trough concentrations? And again, I think that depends on disease phenotype as well as desired outcome. How often should we be performing proactive TDM? And I think most importantly we need a test that’s accurate, accessible and inexpensive, and hopefully covered by insurance. And I would, and I think most people would, like to see some more prospective data on implementation of TDM.

In practice I usually tell people, whatever test you use, know what it is. Can it detect antibodies in the presence of drug? What is the potential cost to your patient? And know what to do with the results. Particularly tricky can be the antibody levels because those differ between each assay. If nothing else, data suggests reactive testing outperforms standard of care, but I still believe proactive testing is likely the best. Why wait until a patient develops antibodies or has loss of response? Check the drug concentrations, optimize the drug, and prevent loss of response from the beginning.
This is a website that can help you. We’re in the process of updating it to have the various drugs, the situations, and what to do with the results.

So now we’ll move on to cases. The first case is a 38-year-old female with longstanding, extensive ulcerative colitis. Despite 6mp with adequate 6 thioguanine levels, she has 2 flares requiring prednisone and is started on infliximab. After 2.5 years of being on combination therapy, she complains that after her last 3 infusions she has some blood on her stools around 6 weeks, which resolve after infusion of infliximab. I’ll point out that all these cases are real patients. The question is: What’s the next step? As we described, this is a secondary loss of response, so you check drug concentrations and antibodies. Here at 6 weeks she has 6 mcg/mL of infliximab and good 6 TG concentration. So the question is: What does this mean, and what do you do? Again, you definitely want to confirm active disease. Here the sigmoidoscopy confirms active proctitis. It looks like a Mayo 2 with some erosions and erythema. So now the question is: What do you recommend? What does the level of 6 in this case mean?

Again, depending on where you look and how you think about it, according to the AGA, the trough concentration of greater than 5 should be adequate. In this case you know that this patient gets better when they get more infliximab, and studies have suggested in some cases infliximab concentrations of greater than 10 may be needed. And in this case, again, this patient is not now in remission, so I chose to dose optimize the patient. Again, I think decreasing the interval now we know is better than increasing the dose, so I decreased the interval to every 6 weeks, repeated the infliximab concentration. Now it was 10.2. The patient did better, and repeat sigmoidoscopy demonstrated mucosal healing.

Dr. Moss.
So, Adam, in this case you have a patient who has symptoms, has endoscopic activity, and their level of infliximab was 6, so you up them and they get to the range of 10. So, in your experience, what are you aiming for the infliximab in terms of levels? What’s the ideal range you like to see your patients’ levels in?

Dr. Cheifetz:
Yes, so again, when I first started, 5 to 10 was the window I was typically aiming for. As I’ve sort of done this more and more and as more data has come out that sometimes higher drug concentrations are associated with better outcomes, I really look at a threshold value. So in most patients I think 5 is probably okay. Right? If you have a patient who’s in deep remission with a trough concentration of 5, that’s great. However, if you scope them where they have other evidence of disease despite being in clinical remission and their level is 5, I will push it higher, closer to 10, and in some cases potentially
even higher. The study from the University of Miami suggests, particularly with fistulous disease, higher concentrations may be needed. And I think it’s important, particularly in the reactive setting, not to give up. I tend not to give up before I can push the levels above sort of 10 to 15. Right? Because in the reactive setting, if you say someone has a therapeutic level, you’re not just giving up on infliximab; you’re really giving up on the entire class.

Dr. Moss:
Okay, great. So, why don’t you tell us about the second case now?

Dr. Cheifetz:
All right. So the second case is a 28-year-old male, who is actually a nurse, with ileocolonic and perianal Crohn’s disease, initially treated with infliximab and azathioprine but transitioned to adalimumab because he was told it was safer while in clinical and endoscopic remission. He initially did well, but then the adalimumab was decreased to monthly and the azathioprine was decreased to 50 mg a day. None of this I would recommend. He presents to me with a moderate-severe flare of Crohn’s confirmed both on radiology with labs and with a colonoscopy, so I very quickly checked levels. Not surprisingly, the adalimumab level was undetectable, and thankfully, he had not yet developed antibodies to adalimumab. I reinduced him with adalimumab and increased his azathioprine back to 100 mg a day. A repeat adalimumab concentration was 7.9, which in most cases is good. He felt better, but I went and I scoped him to confirm he had responded endoscopically, and he had improved, but there was still ongoing endoscopic disease. So, as we’ve sorted mentioned, I then went on to increase his adalimumab to 40 mg weekly. There is definitely some data with adalimumab that drug concentrations of greater than 10 may be associated with better outcomes. Repeat concentration was almost 14 mcg/mL, and then a follow-up was 17. I repeated a colonoscopy, and that confirmed mucosal healing.

Dr. Moss:
Great. So that’s a nice case. One question patients often ask us is: Is there any downside to driving levels high? And what’s your experience or what is the literature? Is there any risk with driving to that higher range?

Dr. Cheifetz:
I tell my patients there has not yet been a study in IBD that suggests that higher drug concentrations are associated with any greater risk of adverse events. In fact, as we’ve talked before, it’s really the low drug concentrations that are associated with antibodies and loss of response. There was 1 study in the rheumatology literature that was a letter to one of the journals which suggested that 3 trough concentrations of infliximab on the order of 25 or more was associated with a slight increased risk of
adverse events. So, again, typically with infliximab, in most cases I’m somewhere between 5 to 10, 5 to 15, and with adalimumab similarly. I think there’s less of a ceiling known, and often times I am aiming sort of certainly greater than 5 and often times, like in this case, greater than 10.

Dr. Moss:
Great. So, finally, let’s go on to your third case then.

Dr. Cheifetz:
So this case is an 18-year-old male, 2 years of extensive Crohn’s ileocolitis and perianal disease. He previously failed azathioprine but is now doing well on infliximab and azathioprine combination therapy. I actually increased his infliximab from 300 to 400 mg due to a trough of 3 mcg/mL. A repeat showed it was more where I wanted it at about 7 mcg/mL. And I confirmed he was in endoscopic remission. This is not uncommon in those patients on combination therapy. They come; it was about 6 months later he says, “Doc, can I stop the azathioprine?” or, “I want to stop the azathioprine.” Often times they’ll just stop it on their own. So, basically, here I’ll have a conversation with the patient and go over what happens when we stop azathioprine. And again, this, to me, is partially the concept of optimized monotherapy.

In this case I wanted to make sure his trough was still adequate before we did anything, and it was 6.5 mcg/mL, so still in a decent range. However, we know from studies, particularly a study by Tedesco* that was presented at DDW a few years ago, in a group on combination therapy, when you stop the azathioprine, the median trough concentration of infliximab fell from about 4 to about 2, and up to about 40% of patients had undetectable trough concentrations and a greater number antibody formation than the group that stayed on combination therapy or just had half of the azathioprine. So I always tell patients, if we stop the azathioprine, we’re going to expect the infliximab trough concentration to fall.

So in this case the options are just to tell him, “Stay on both drugs and we’ll see in a little bit.” Decrease the interval to 7 weeks, stop the azathioprine, sort of overcome the expected decrease in trough by decreasing the interval, increase the dose of the infliximab further and stop the azathioprine or just stop the azathioprine and see how much it falls. I wouldn’t be in favor of the latter with an infliximab concentration of 6.5. My guess is that it would drop below 5 mcg/mL. Whatever we do or you do, again, I would recommend closely following these infliximab concentrations and antibodies. Again, in this case we decreased his interval to 7 and stopped the azathioprine. He really wanted to come off. A repeat trough was 7 mcg/mL, and we continued to just follow him closely on, again, what I term optimized monotherapy with infliximab.

Dr. Moss:
Great. So I think most patients would be reassured to know that that’s a way of determining have there been any downsides to withdrawing the azathioprine to be able to monitor their levels on follow-up.

Well, this has been a great case presentation with certainly plenty of key takeaway points for the audience to better treat our patients with IBD. I am Alan Moss, a gastroenterologist at Beth Israel Deaconess Medical Center in Boston.

Dr. Cheifetz:
And I’m Adam Cheifetz, also at Beth Israel Deaconess Medical Center in Boston. Thank you for joining us.

Dr. Moss:
Take care, everyone.

Announcer:
The preceding activity was jointly provided by Postgraduate Institute for Medicine and Medtelligence. To receive your free CME credit, be sure to complete the post test and evaluation, by visiting ReachMD.com/Medtelligence.
ReachMD: Be Part of the Knowledge.