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Evaluating Therapeutic Drug Monitoring in IBD

Dr. Buch:
Therapeutic drug monitoring is used to monitor drug doses and adjust accordingly based on their concentrations to avoid toxicity and to improve efficacy. The monitoring of anti-tumor necrosis medications has emerged as an important tool to optimize therapy for patients with inflammatory bowel disease, or IBD for short. What do we need to know about it?

This is *GI Insights* on ReachMD. I'm your host, Dr. Peter Buch. And joining me today to take a look at therapeutic drug monitoring, also known as TDM, is Dr. Adam, Cheifetz, who is Professor of Medicine at Harvard Medical School. Dr. Cheifetz is also Director of the Center for Inflammatory Bowel Disease at Beth Israel Deaconess Medical Center and the lead author of "A Comprehensive Literature Review and Expert Consensus Statement on Therapeutic Drug Monitoring of Biologics in Inflammatory Bowel Disease" published in The American Journal of Gastroenterology.

Welcome to the program, Dr. Cheifetz.

Dr. Cheifetz:
Thank you, Peter. I really appreciate it, and I appreciate being here today.

Dr. Buch:
To start us off, can you tell us why therapeutic drug monitoring is important for our IBD patients?

Dr. Cheifetz:
Absolutely. I think TDM is extremely important for our patients with IBD, particularly those on anti-TNF therapy. And throughout most of this discussion, I will focus on the anti-TNFs. I think TDM, you know, really falls within a group of other treatment paradigms that many of us have been doing recently in order to improve the outcomes for our patients, in addition to—You know, we talk about treating patients earlier, before their disease, before they can get complications, before they get strictures or a fistula or cancer, treating them more effectively with agents that actually work. Again, we talk about goals of care, treating deeper, aiming for at least mucosal improvement as well as improvement in faecal calprotectin and, and CRP. And I think if you're going to use an agent, you may as well optimize it and get everything you can out of it, and I think that is where TDM comes in.

Unfortunately, although anti-TNF therapies have really revolutionized how we care for our patients with IBD and how they do, unfortunately, 30 percent of patients still have a primary nonresponse to anti-TNF therapies, and over time, over 50 percent of patients will have a secondary loss of response, and I think that TDM, is a way to improve those outcomes. Particularly, for anti-TNF therapies, I would still argue that infliximab is still our most effective agent in our sickest patients with inflammatory bowel disease or hospitalized patients with ulcerative colitis or Crohn's disease patients that have severe disease, or perianal disease, so, when we put these patients on it, we really want to optimize it.

When we talk about TDM, we really are talking about two different things: reactive TDM and proactive TDM. Reactive therapeutic drug monitoring or checking drug concentrations when someone has a flare of IBD has really been shown to rationalize care in IBD and better direct management, giving more drug to a patient who's going to benefit from it and switching medications in someone who's not going to benefit from more drug. It's been shown to be more cost-effective than empiric dose escalation, and it's been associated with better outcomes than empiric dose escalation. I think reactive TDM is really standard of care at this point. What I'd really like to focus on is proactive TDM, which is dosing to a therapeutic concentration from the beginning. When you start someone on the drug, make sure they have enough drug on board. If they don't, give them more drug.

This isn't a new concept. We've been doing this—I, certainly, throughout medical school and residency, checking vancomycin drug

concentrations, gentamicin, certainly during my fellowship in use of cyclosporine, tacrolimus. Again, it's not a new concept.

Dr. Buch:
Do you think that we should be doing therapeutic drug monitoring on all of our patients with IBD?

Dr. Cheifetz:
Yeah. So, if you ask me, I would say absolutely, but I will be the first one to admit I'm extremely passionate about this subject, and some would use the word biased. I do think all patients could benefit from TDM. And, you know, usually, when someone asks me that, I'll say, 'Well, you have a liver transplant on tacrolimus. Do you think all your liver transplant patients will benefit from TDM or checking tacrolimus levels?' And in that case the answer is yes. Both for therapeutic levels you want to make sure they have enough drug on board, and with certain drugs like tacro-cyclosporine, too much drug above a certain concentration is actually detrimental and has a higher risk of adverse events. That's not been shown to be the case with anti-TNF therapy.

So let's take a step back. Let's say it's not me who would say to do it in everybody. The recommendations from the consensus panel that you mentioned published last year in American Journal of Gastroenterology would say for reactive testing it is recommended in all patients with primary nonresponse or secondary loss of response, and that included both anti-TNF therapies as well as our newer therapies, vedolizumab and ustekinumab. Another important thing we mentioned with reactive testing is, is really to make sure when you're checking reactively you don't give up too easily on a medication and that drug concentrations for infliximab and adalimumab, which are used most frequently, should be more than 10 to 15 before moving on to another agent.

For proactive therapeutic drug monitoring, the consensus panel recommended doing this in patients on anti-TNF therapy after induction, post induction, and at least once during maintenance therapy. They also recommended it after reactive TDM. Also, it was recommended when considering combination therapy with an immunomodulator, as I discussed, and we did get slightly into the role of optimized monotherapy as an alternative to combination therapy with an immunomodulator in some patients with anti-TNF therapy. The other role it was recommended for is during infliximab de-escalation or stopping an immunomodulator when it's being considered. And again, you want to check it before you stop an immunomodulator or before you de-escalate infliximab or adalimumab or whatever drug to make sure you have enough drug on board.

Dr. Buch:
Again, that was excellent. For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Adam Cheifetz about therapeutic drug monitoring in inflammatory bowel disease.

Let's switch gears a bit here, Dr. Cheifetz. Can you tell us what factors are associated with a lower drug concentration in IBD?

Dr. Cheifetz:
Absolutely. So, those patients that have more severely active disease, those patients with a low albumin, high CRP, high baseline TNF, those are the patients that very rapidly clear anti-TNF therapies and have lower drug concentrations. Certainly, the presence of anti-drug antibodies to anti-TNF therapies increase clearance and therefore decrease drug concentrations. High BMI and male sex also appear to be associated with higher clearance and lower drug concentrations in inflammatory bowel disease. And more recently, HLA-DQA1*05, which is seen in about 40 percent of patients of sort of more, West European descent with infliximab and adalimumab, that has been associated with anti-drug antibodies and loss of response, and some people have taken to checking that prior to starting anti-TNF therapies.

Dr. Buch:
So, before we conclude, are there any other thoughts you'd like to share with our audience today?

Dr. Cheifetz:
I think, one, just think about TDM. You know, certainly, I would recommend doing it reactively. Again, it just better tells you which patients need more drug and which patients need to move on. But I would strongly consider proactive therapeutic drug monitoring. I really do feel the data is there, and there's more and more data, prospective data now, randomized controlled trials that do show it is effective, and I really think it's important for our patients in order to better optimize them.

And I will throw a plug in for a trial. We got funding to do a multicenter trial called the OPTIMIZE trial, which will randomize patients with moderate to severely active Crohn's disease to either standard of care, which we defined as monotherapy, or combination therapy with infliximab 5 mg/kg at 026 and every eight weeks versus the interventional group, which is optimized monotherapy utilizing a PK dashboard starting at week two, and seeing which group outperforms. Our theory is that the optimized group will actually outperform the standard of care group. And we're also, obviously, looking at safety as well.

Dr. Buch:

That sounds extremely exciting. So, if any of our listeners have a patient they want to enroll, how should they do it?

Dr. Cheifetz:
Well, listen, if anybody out there is part of a big private practice and you do research and you want to get involved, please e-mail me. We still are looking for some sites. Certainly, if you're at academic institutions and they're using a lot of infliximab, you can e-mail me. It's A-C-H-E-I-F, as in Frank, E-T at B-I-D-M-C dot Harvard dot E-D-U. And if you're in any areas where there are sites up and running, please feel free to send your patients in.

Dr. Buch:
That's great. With those considerations in mind, I want to thank my guest, Dr. Adam Cheifetz, for an excellent discussion on therapeutic drug monitoring in inflammatory bowel disease. Dr. Cheifetz, it was a pleasure having you on the program.

Dr. Cheifetz:
Listen, Peter, it was my pleasure. I appreciate you having me.

Dr. Buch:
For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit reachmd.com/giinsights, where you can Be Part of the Knowledge. Thanks for listening, and see you next time.