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Exploring Therapeutic Drug Monitoring in IBD

**Dr. Nandi:**
Welcome to IBD Crosstalk for *GI Insights* on ReachMD. I'm your host, Dr. Neil Nandi. And joining me today to share some of his intriguing research on therapeutic drug monitoring in IBD is Dr. Andres Yarur from Cedars-Sinai in LA. Now, Dr. Yarur is an Associate Professor of Medicine and an IBD extraordinaire. His research has pioneered new insights into how we understand to utilize therapeutic drug monitoring in our inflammatory bowel disease patients.

Andres, welcome to the program.

**Dr. Yarur:**
Well, thank you so much for inviting me, Neil.

**Dr. Nandi:**
You know, you've done years of focused research in this space, and we've really come a long way, and I think discussing how we use therapeutic drug monitoring drug by drug is important because we have an expanding armamentarium, and I think it's important that we clinicians kind of review, you know, when to use it and how not to use it. So let's just first step back and say how common is drug antibody formation for biologics by the biologic?

**Dr. Yarur:**
That's a great question, and I think at a high level, as you mentioned, every drug is a little bit different. And things have really changed and evolved in the last 10 to 15 years. So, when we talk about one biologic, such as infliximab, things are very different when compared to newer biologics, such as, let's say, risankizumab or ustekinumab where molecularly. And we go all the way to the biology, they are very different. So, immunogenicity or the development of antibodies against these biologics started being a very big problem especially at the very beginning where clinicians were using infliximab in intermittent basis. So patients would get a dose of infliximab, they would feel better, and then they would not get a scheduled maintenance. But they would just get an as-needed dose. And one of the big problems with that strategy is that it was very common for people to develop antibodies to drug, and that translated in the drug not working, that translated into infusion reactions and other adverse events, and that's why it came this scheduled regimen, which is how we use infliximab now.

In general, even using the drug in a scheduled type of strategy where, like I was saying, as we do now, the antibody formation is still quite high, and we're talking about 10 to 15 percent. The episodic strategy at the very beginning, about 40 percent of patients develop antibodies. So it is true that by using the drug on a regular basis, and scheduled irrespectively, if the patient is feeling well or not decreases the chance of getting antibodies but still very high.

**Dr. Nandi:**
Let me ask you, how does inflammation play a role with TNFs? Right? When you have active disease in the gut, what is its impact on drug levels? And does it differ between the different TNF agents?

**Dr. Yarur:**
So, in general, active inflammation has always been correlated with a lower level, and that's one of the common conceptions and observations that we have seen, right? So patients with a high burden of inflammation have lower drug levels, for the most part, and inflammation drives levels down due to several reasons. One is that when there's systemic inflammation in the body, that increases the catabolism of proteins at a cellular level, so that's the number one reason. Number two, with inflammation in the bowel, there's a protein-losing enteropathy in where patients actually lose the drug through the bowel, and that has actually been studied in this with infliximab,


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so that's another important reason. And a third reason that could potentially explain that there is an anti-TNF sink by high amount of TNF expression in the actual tissue.

**Dr. Nandi:**
When it comes to anti-TNF PK, pharmacokinetics, are there other factors that affect it? And I know the answer is yes. And are any of them modifiable?

**Dr. Yarur:**
Definitely. There are several factors that can increase the clearance of drug as we mentioned a few minutes ago. And one of the most important ones are the presence of anti-drug antibody. So these anti-drug antibodies increase the clearance of drug and drive the drug levels down. That's unfortunately a common observation. And other factors is the concomitant use of immunosuppressants, such as azathioprine or mercaptopurine and methotrexate which decrease the chance of developing antibodies. So indirectly, you're decreasing the clearance, but also, there are studies that have shown that there's a synergy, and the patients irrespectively if they have antibodies or not tend to achieve higher drug levels.

**Dr. Nandi:**
So, you know, if I understand this better, I believe if you're just trying to optimize drug levels, that there seems to be benefit to combining TNFs with thiopurines, but it doesn't seem to translate when we look at other agents, such as vedo or ustekinumab. Is that about right to say?

**Dr. Yarur:**
That's correct. I mean, there are no randomized controlled trials yet, but there is, I would say, enough evidence that has shown that combination therapy of the biologics, other biologics that are non-anti-TNF, we don't see that benefit that we see with anti-TNF. And that probably has a lot to do with the fact that the immunogenicity against the other biologics is not as high. It's actually quite low. And it also has to do potentially with pharmacokinetic differences, half-life. Even maybe mechanisms of how the drug works are different too, but as of now the observation is that the combination therapy does really not improve the pharmacokinetics of these drugs.

**Dr. Nandi:**
So, you know, now that we've kind of set the stage, right? What do most studies show the immunogenicity or drug antibody formation is for vedolizumab or ustekinumab? And is there any data for a newer agent to our realm in 2022, such as risankizumab?

**Dr. Yarur:**
In terms of what we know about vedolizumab, for example, which was the first non-anti-TNF biologic approved in IBD, the prevalence of antibodies in the population is quite low, and there's a few studies about it. And irrespectively of the assay used, the rate is about 3 percent. And not only slow but also a lot of these antibodies really don't have clinical significance. Some of them actually do and are correlated with lower drug levels, but in all honesty, the real neutralizing antibody rate is even probably lower than 3 percent. But we're talking about between two and four percent.

**Dr. Nandi:**
For those just tuning in, you're listening to *GI Insights* IBD Crosstalk on ReachMD. I'm Dr. Neil Nandi, and I'm speaking with Dr. Andres Yarur about therapeutic drug monitoring in IBD in the year 2022.

So, Andres, we have a new agent this year, new to Crohn's realm, which is risankizumab. Do we know much about therapeutic drug monitoring or levels or optimization with risankizumab yet?

**Dr. Yarur:**
As of now it's still really unclear. As the drug became available a few months ago and we have more experience in the real world, and we have commercially available assays to measure this we will learn. I think it's still too early to make a statement on that.

**Dr. Nandi:**
You know, there's this concept of proactive versus reactive TDM. Right? It's always this ongoing debate. In a nutshell, what is your approach or stance on how you decide when to do proactive versus reactive TDM? What would you advise?

**Dr. Yarur:**
So, in general, someone that has started treatment with an anti-TNF and especially with infliximab where the dosing is more flexible, you can have a patient that obviously either doesn't respond to the drug or loses response to the drug after entering remission, or as a third option they have a partial response. And in that scenario is where we apply therapeutic drug monitoring, measuring the levels, measuring the presence of anti-drug antibodies to try to understand if maybe that person that has lost response is because they developed antibodies or because their drug level is low. And that's what we call reactive, so it's reactive to a nonresponse. And on


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those cases, the study and the data have shown that by increasing the exposure a lot of these patients can recapture response. And again I want to stress that this is with anti-TNF.

**Dr. Nandi:**
What can you tell us about vedolizumab and trying to dose-optimize and utilize drug levels?

**Dr. Yarur:**
So there are multiple studies, and we have done this also multiple times, that have shown that higher drug levels, specifically higher vedolizumab drug levels, are associated with better outcomes, short-term outcomes and long-term outcomes, but that has really been an association. And the INTERPRET study tried to answer the question if the drug levels with a patient has low vedolizumab drug levels is clearing the drug at a high rate for whatever reason. What happens if we increase the dose? Can we make these patients actually respond to the drug? So it really proved the concept wrong that just by increasing the exposure doesn't mean that you're going to increase the response, which is something that we have seen with anti-TNF for sure, but that did not apply to vedolizumab.

**Dr. Nandi:**
What can you tell us about reactive TDM when it comes to ustekinumab?

**Dr. Yarur:**
I think with ustekinumab, something similar happens. I mean, as of now, there's no data available. There is a study that is ongoing that is trying to see if increasing the exposure can rescue some patients. I think that in general we also have to distinguish between complete nonresponders versus patients that lose response. My approach with vedolizumab in a patient that does not respond at all, I tend to just leave them on the drug, on the standard dose, and see if they actually capture response later on. In loss of response I think it's a little bit different, and INTERPRET doesn't necessarily apply to those patients because we don't know if that loss of response mechanism is the same as a complete nonresponse, so I still dose escalate.

Again, it's really unknown, and obviously, as physicians we want our patients to do well, and we have limited drugs, and many of the patients have been on several drugs, so until we have more data and there's, I would say, observational data that some patients respond to dose escalation. I am trying dose escalation to every four weeks when possible, but we still need more data.

**Dr. Nandi:**
Before we close, do you have any last pearls or points that you'd like to convey to our listeners?

**Dr. Yarur:**
Very briefly. We talked about reactive therapeutic drug monitoring for anti-TNF, and then this again applies only for anti-TNF. I think that even though there are studies that have shown that proactive TDM does not improve outcomes. I think that it's a very difficult question to answer. And a lot of patients with a more aggressive disease still benefit from proactive therapeutic drug monitoring, so patients with, let's say, severe ulcerative colitis, fistulizing disease, and Crohn's, I think it's still reasonable. And I think it's part of personalizing medicine that in certain patients when need to be a little bit more aggressive.

**Dr. Nandi:**
I think you're right. You're absolutely right. Dr. Yarur, thank you so much for your time and wisdom. You have put so much time into this research. You are the perfect person to speak with on this topic. I really appreciate you coming on our program.

**Dr. Yarur:**
Well, thank you so much, again, for the invitation. It was really a pleasure.

**Dr. Nandi:**
Thank you. For ReachMD's IBD Crosstalk, I'm Dr. Neil Nandi. To access this and other episodes in this series, please visit ReachMD.com/GIInsights where you can be Part of the Knowledge. Until next time, thanks for listening.


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