ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Overview of Therapeutic Drug Monitoring of Biologic Agents in Patients With Inflammatory Bowel Disease

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G&H What is the goal of therapeutic drug monitoring?

AC From my perspective, the goal of therapeutic drug monitoring (TDM) is to optimize the care of patients with inflammatory bowel disease (IBD). Better utilization of TDM has the potential to improve the efficacy, safety, and cost-effectiveness of biologic therapies.

G&H Why is TDM important to use when managing patients taking biologic agents?

AC TDM is not a new concept; it has been done for years with different medications. For instance, different antibiotics (eg, vancomycin and gentamicin) and certain immunosuppressants (eg, tacrolimus) are dosed to a therapeutic window, and if they are above a certain threshold, they become toxic; however, if they are below the threshold, they are not effective. Even in IBD, for example when cyclosporine is used to treat severe ulcerative colitis, it is standard to dose the patient to a specific therapeutic window.

With certain drugs, it is the ceiling of the therapeutic window that is the most important because the drug becomes toxic above a certain level. With biologic agents, only one small study has suggested that very high drug concentrations in patients with ankylosing spondylitis are associated with an increased risk of infections. It is really the low drug concentrations that are problematic and associated with antibody development and loss of response. A number of cross-sectional studies and post-hoc analyses of randomized, controlled trials have shown that, as expected, higher drug concentrations of biologic agents are associated with better outcomes and that undetectable drug concentrations are associated with poor outcomes, including loss of response. In fact, higher trough concentrations typically correlate with more objective and harder-to-reach outcomes such as mucosal healing. Thus, patients on biologic agents should be kept above that undetectable drug concentration; typically in my practice, for patients in the maintenance phase, I aim for a drug concentration greater than 5 µg/mL for infliximab (Remicade, Janssen) and greater than 5 to 12 µg/mL for adalimumab (Humira, AbbVie). However, there is much research yet to be done on optimal trough concentration windows in IBD.

G&H Should TDM be used in all IBD patients on biologic therapy?

AC I think TDM should be used in all patients. It is somewhat disappointing how patients respond to biologic therapies. In most phase 3 trials of anti–tumor necrosis factor (TNF) agents, only approximately two-thirds of patients respond initially, and then upward of half of those patients lose response over the first year and another 10% to 15% of patients lose response each year thereafter. Thus, with standard dosing, anti-TNF therapies do not have good long-term persistence, and a lot of that is likely due to subtherapeutic drug concentrations and the development of antidrug antibodies. Early utilization of TDM and dose optimization during the induction phase

and continuing to dose to a therapeutic window in the maintenance phase could prevent some primary nonresponse and, more importantly, a good deal of secondary loss of response.

G&H When exactly is the optimal time to measure drug concentrations in patients?

AC Typically, TDM involves checking a trough concentration right before the next dose of the drug. This often gives the physician the most valuable information and is most important with intravenous medications (eg, infliximab) with a high peak and true trough. However, when performing TDM reactively, which is how most physicians currently use TDM, physicians do not have to wait until the trough.

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An important aspect of this issue of timing relates to whether physicians should be checking drug concentrations during the maintenance phase as well as during the induction phase or just waiting until patients are losing response to medications. Reactive TDM is more cost-effective than empiric dose escalation, but recent studies suggest proactive TDM (in the maintenance phase) is better than reactive TDM or empiric dose escalation. However, it may turn out that optimization during the induction phase is most important.

G&H What have studies reported specifically regarding the use of reactive TDM?

AC Reactive TDM was shown to be more cost-effective than just empiric dose escalation or standard of care in a modeling study by Velayos and colleagues and a European study by Steenholdt and colleagues. Other studies have shown that reactive TDM better directs care. This method gives more drug to patients who need more drug and not to those who require a different medication (or surgery). However, the most important aspect of reactive TDM is proving objectively that the patient's gastrointestinal symptoms are due to active IBD and not another etiology.

G&H What studies have been conducted on the use of proactive TDM?

AC In my opinion, proactive TDM is where the field needs to be heading to improve both short- and long-term outcomes of patients. There have been several studies on this method. The largest and most well-known study is the landmark TAXIT (Trough Level Adapted Infliximab Treatment) trial, which is often misquoted as a negative study and a reason not to perform proactive TDM. However, that was not really the conclusion of the authors. The problem with the TAXIT trial was that it had design flaws and, therefore, missed its primary endpoint.

The TAXIT trial was a Belgian study in which all of the patients were stable (ie, in stable clinical response or in clinical remission) and were dose-optimized to their defined therapeutic window of 3 to 7 μg/mL. If a patient's drug concentration was lower than the window, he or she was given more drug, and if the drug concentration was higher, the dosing interval was spread out or the dose was decreased. If a patient was in the therapeutic window, he or she was left alone. Only after dose optimization into the therapeutic window were the patients randomized to 1 of 2 groups: continued dose optimization and proactive TDM, or standard of care (ie, dosing based on clinical symptoms and C-reactive protein levels). Importantly, after this initial dose optimization, in patients with Crohn's disease who had low drug concentrations, the researchers were able to capture approximately 15% of patients who were just responding and were able to induce remission. In these patients, there was also improvement in C-reactive protein levels.

However, after the patients were dose-optimized, they were followed only for a year. Thus, the primary endpoint, which was remission at 1 year, was no different between the 2 groups. Nevertheless, there were other secondary endpoints that clearly favored the group that was being treated based on trough concentrations. Fewer patients in that group had a flare of their disease as well as undetectable trough concentrations. Because the primary endpoint was missed, I think people are under the impression that the study showed that proactive TDM did not work. In actuality, it did work because at the time of dose optimization, 15% of patients entered remission, and the other secondary outcomes favored continued dose optimization. Thus, this study demonstrates that one-time proactive dose optimization improves outcomes in patients with Crohn's disease and low trough concentrations and that continuing proactive TDM is associated with fewer flares of IBD in the first year of follow-up.

In 2014, my colleagues and I published the results of a study that was similar to the TAXIT trial, in that

patients were dose-optimized to a therapeutic window (5 to 10 µg/mL in our study). We compared that group of patients to a group of patients from our IBD center who were receiving standard of care (either empiric dose escalation or reactive TDM). There was much greater persistence on infliximab in the group of patients undergoing proactive TDM. That is why I have continued to use proactive TDM in clinical practice.

In addition, my colleagues and I, along with researchers from the University of Pennsylvania, performed a study, currently online at *Clinical Gastroenterology and Hepatology*, in which we looked at over 250 patients who had undergone either proactive or reactive TDM. Patients were separated into these 2 groups based on the first test they had undergone (reactive vs proactive). Looking at the outcomes, we found that there was much less drug discontinuation in the group that had undergone proactive TDM as well as fewer IBD-related hospitalizations and surgeries, fewer serious infusion reactions, and less development of antibodies to infliximab. These objective endpoints suggest that proactive TDM is likely better than just waiting until patients have symptoms and then testing patients reactively.

G&H Currently, how common is TDM of biologic agents in general and in terms of the 2 different testing methods?

AC As of yet, there are no published studies assessing how commonly physicians are utilizing TDM overall. In practice, if gastroenterologists are using TDM, they are using it reactively as opposed to proactively. My hope is that proactive TDM will become more commonplace, if not the standard of care. As previously discussed, data suggest that outcomes with proactive TDM are better than with reactive testing or empiric dose escalation. In my opinion, proactive TDM is not being used as much as it should be, possibly because of lack of knowledge or, more likely, the fear that the test will result in an out-of-pocket cost to the patient.

> ... it is important to check drug concentrations before and then after stopping immunomodulator use in patients on combination therapy.

G&H What are the main challenges associated with TDM of biologic agents?

AC One challenge is that the optimal trough concentration windows are not well defined. Most of the data currently available are from the maintenance phase, although TDM is probably more important to perform during the induction phase. It is during this phase that patients are the sickest and likely require the most drug.

Another challenge involves the test itself. There is still a need for a test that is accurate, accessible, and inexpensive with which to perform TDM. The best test would be quick and could be administered at the point of care; this way, the physician could perform the test during an office visit or just prior to the infusion and make a change before giving the patient the next dose. Currently, when physicians check drug concentrations, they usually do not know the results for approximately a week, at which point they have already given the next dose of the drug.

G&H How can TDM actually be utilized in clinical practice?

AC As discussed previously, reactive TDM has been demonstrated to be better than empiric dose escalation, as it better directs care and is more cost-effective, but proactive TDM is likely more important in optimizing the care of patients with IBD. Also as mentioned, I think that we are going to learn that it is during the induction phase that TDM is most important. In fact, Papamichael and colleagues showed that infliximab or adalimumab concentrations during or just after induction therapy are associated with early mucosal healing in patients with ulcerative colitis. Moreover, week 14 infliximab concentrations were associated with persistent remission at week 52 in a study by senior author Dubinsky and colleagues.

Additionally, it is important to check drug concentrations before and then after stopping immunomodulator use in patients on combination therapy. I typically utilize optimized biologic monotherapy or proactive TDM while patients are on a single biologic (without a concomitant immunomodulator). There are data, particularly from the SONIC (Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease) trial, that combination therapy is associated with better outcomes than monotherapy with infliximab. However, there was recently a reanalysis of SONIC by Hanauer and colleagues, presented at this year's Digestive Disease Week, which suggested that concomitant immunomodulator use increased the trough concentration of infliximab and

that the trough concentration, not necessarily immunomodulator use, actually correlated with better outcomes. In the first study of proactive TDM by my colleagues and I, 31 patients of the original cohort were either on monotherapy the entire time or went from combination therapy down to monotherapy with infliximab and had a trough concentration greater than 3 µg/mL (typically >5 µg/mL); no patients lost response over a median follow-up of over 3.5 years.

In addition, the BRIDGe Group, of which I am a part, used RAND methodology to develop recommendations for whether something is appropriate or inappropriate on a scale of 1 to 9, with 1 to 3 being inappropriate, 4 to 6 being uncertain, and 7 to 9 being appropriate. We wanted to determine if and when it was appropriate to perform TDM and found that TDM was appropriate in most situations: at the end of induction in patients with primary nonresponse, in patients with secondary nonresponse, during maintenance and response (ie, proactive TDM), and when restarting therapy after a drug holiday before the second infusion. The only time we found use of TDM to be uncertain was at the end of induction in responders. We did not find TDM to be inappropriate in any situation. Furthermore, we made recommendations as far as what was inappropriate, appropriate, or uncertain regarding decisions based on various clinical scenarios, drug concentrations, and antibody levels, and what to do with the results. This information was published in *Clinical Gastroenterology and Hepatology*, and an "anti-TNF optimizer" is available on the group's website (www.BRIDGeIBD.com). There, physicians can select a drug, concentration, antibody level, and clinical scenario, and then see if the group thinks whether a certain action is appropriate, inappropriate, or uncertain.

G&H What are the next steps in research in this area?

AC The most important next step is likely conducting a prospective analysis of proactive TDM vs standard of care. In addition, as previously mentioned, we also need to better define therapeutic windows.

Dr Cheifetz has consulted for Janssen, AbbVie, Pfizer, Takeda, Miraca Laboratories, Ferring, and AMAG.

Suggested Reading

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