CLINICAL REVIEW

Therapeutic Drug Monitoring in Inflammatory Bowel Disease

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Introduction

Therapeutic drug monitoring (TDM) is the clinical practice of measuring a specific drug or active metabolite levels and if pertinent, anti-drug antibodies. This is especially important in optimizing therapy in patients with inflammatory bowel disease (IBD), including both ulcerative colitis (UC) and Crohn's disease (CD). There are two types of therapeutic drug monitoring. Reactive therapeutic drug monitoring refers to measurements in response to disease activity to understand reasons for poor response and inform treatment change.[1] Alternatively, proactive therapeutic drug monitoring involves checking drug levels in the absence of a change in clinical status.[2] The purpose is to guide ongoing treatment to avoid treatment failure. There is current debate on how we should be performing therapeutic drug monitoring in IBD patients.

Why is therapeutic drug monitoring important? Because one size does not fit all. The dose of drug required to achieve therapeutic levels varies for different patients based on multiple factors. A study 2012 examined various pharmacokinetic factors that can impact anti-tumor necrosis factor (anti-TNF) drug clearance in IBD.[3] Increased clearance was associated with presence of anti-drug antibodies, high body mass index, male gender, and a pro-inflammatory state measured by a high baseline TNF, high C-reactive protein (CRP), and low albumin. These factors increased drug clearance and led to lower drug levels. One factor – use of immunomodulators - decreased drug clearance and led to higher levels of the drug.

Thiopurines

We will review therapeutic drug monitoring as it relates to thiopurines. This class of medications is used in IBD patients to maintain quiescent disease and prevent antibody formation. The current American Gastroenterological Association (AGA) currently proposes routine TPMT monitoring in adults with IBD started on thiopurines. TPMT testing. In adults treated with thiopurines with active IBD or with potential thiopurine or adverse effects, the AGA suggests thiopurine metabolite monitoring to guide treatment change changes a form of reactive drug monitoring. However, in adults with quiescent IBD treated with thiopurines, the AGA suggests against thiopurine metabolite monitoring, which is a form of proactive drug monitoring.[1] To understand the importance of drug monitoring with thiopurines, we will review the thiopurine pathway. Azathioprine is a prodrug used to treated IBD. About 88% of it is converted to 6-mercaptopurine (6MP) in red blood cells, which is why it is dosed higher at 2.5 mg/kg as compared to 6MP, which is dosed 1-1.5mg/kg (4). 6MP is then metabolized in one of three competing pathways. It may be methylated by the TPMT enzyme into 6MMP, which has hepatotoxicity, this is why it is important to measure TPMT activity prior to starting a thiopurine.[5] Some is broken down into 6-thio-IMP and eventually to 6-thioguanine (6TG), the therapeutic metabolite. At high doses, it can lead to myelosuppression, or more typically leukopenia. Lastly, 6MP can get metabolized to an inactive metabolite (6-thiouric acid) via the enzyme xanthine oxidase.[4] Two potential drugs can impact this pathway by increasing the therapeutic metabolite, 6TG, are allopurinol and 5-aminosalicylic acid (5-ASA). Allopurinol blocks xanthine oxidase and stops the shunting of drug down the inactive 6-thiouric acid pathway and preferentially toward to the 6TG pathway as opposed to the 6MMP pathway. Why there is a preference toward 6TG versus 6MMP is incompletely understood. Because it will increase 6TG levels and to some extent, 6MMP levels, it is recommended to lower the thiopurine dose before starting allopurinol to avoid hepatoxicity and myelosuppression. 5-ASA drugs can reversibly inhibit TPMT, leading to higher 6TG levels, and increased risk of myelosuppression. This is less frequently used because of weak inhibitory effects.[4] What are the target values for thiopurine metabolites? Multiple studies suggest that a 6TG value of 230-260 is associated with clinical remission in both adults and children. Values greater than 450 were associated with myelosuppression.[6] For combination therapy, a value greater than 125 was associated with higher IFX levels and clinical remission, a lower target level than monotherapy. For 6-MMP, a drug level greater than 5700 was associated with a three-fold risk of hepatotoxicity.[6]

In addition to measuring metabolite levels, it is important to measure TPMT levels prior to initiating a thiopurine, as recommended by the AGA. The lower the TPMT level, the higher the leukopenia risk as more is shunted toward the 6TG pathway. TPMT can be measured through genotype or phenotype testing, although the latter is more commonly used because it has better predictive value. However, there are two scenarios where the genotype would be more appropriate as TPMT measured in red blood cells. Patients with uremia with a high BUN or patients with a recent blood transfusion.[5] Ninety percent of the population has normal TPMT activity. However, 10% of the population has intermediate activity and it is recommended to reduce the starting dose by 50%. About 0.3% of the population has low activity, and another therapy should

be considered. Serial CBC should still be monitored as that majority of patients who develop leukopenia have normal TPMT production.[5]

With understanding of TPMT activity and metabolite levels, clinician can manage patients with IBD on thiopurines in different clinical scenarios. The first scenario is low or absent 6TG and 6MMP levels. This may suggest nonadherence to therapy. Clinicians should provide education on the importance of compliance. Low levels can also result from underdosing. The dose should be increased and the levels, rechecked. The second scenario is when the metabolites show a low 6TG and a high 6MMP. Up to 24% of patients preferentially produce 6MMP while maintaining low levels of 6TG despite increasing the dose. These patients are labeled as "thiopurine resistant." A possible solution is to add allopurinol since it preferentially shunts more 6MP to 6TG as opposed to 6MMP, while lowering the dose to prevent myelosuppression.[7] Another strategy is to split thiopurine into twice daily dosing. A retrospective study in patients with preferential 6MMP metabolism showed the dividing the daily dose of the thiopurine modifies how the drug is metabolized, resulting in significant reductions in 6MMP levels.[8] The last clinical scenario is when a patient has high 6TG levels and high 6MMP levels. These patients are considered "thiopurine refractory" and the best management is to switch to another therapy.[7,8]

Biologics – Reactive Therapeutic Drug Monitoring

Biologics are an important medication class in treatment of IBD, and monitoring drug levels of various biologics has been important in inducing and maintaining remission. Many studies and meta-analyses show the higher the biologic drug level, the better the outcomes. For example, a prospective cohort study followed 90 patients with Crohn's disease on maintenance Infliximab (IFX) demonstrated a higher proportion of patients with a detectable trough serum infliximab level achieved complete interval clinical remission, biochemical remission and endoscopic improvement compared to the group with an undetectable infliximab trough level.[9] The AGA recommends that adults with active IBD on anti-TNF therapy should have, reactive drug monitoring to guide treatment.[1]

Reactive therapeutic drug monitoring is widely accepted. Up to 30% of patients will have a primary nonresponse to a biologic, and up to 50% of patients will experience a secondary loss of response to a biologic.[2] In these situations checking drug and antibody levels help develop the next action plan instead of empirical dose escalating or switching to another drug, which can be more costly and ineffective.[10] Only one randomized controlled trial compared reactive therapeutic drug monitoring to empiric dose escalation.[11] It involved 69 patients with Crohn's disease on maintenance IFX who had active disease and were randomized to either reactive drug monitoring or empiric dose escalation. Twelve weeks later, they found no difference in rates of clinical remission. However, a significant limitation of this study was the definition of optimal IFX trough as >0.5mg/ml. Any patients above this level were deemed as failures to treatment and switched to an alternative non-TNF based therapy. Many of these patients with subtherapeutic levels, simply needed to have dose escalated. This study provided limited quality evidence. Although this was the only randomized controlled trial on reactive drug monitoring, there have been multiple small observation studies showing better outcomes with reactive drug monitoring as compared to empiric dose escalation or drug switching. A modeling study in 2013 demonstrated reactive drug monitoring was more cost effective and better directs care than empiric dose escalation.[12] This cost effectiveness study was supported by a randomized controlled multicenter study published in the same year, which demonstrated 56% lower cost in the reactive therapeutic drug monitoring group.[11]

Individuals experiencing worsening symptoms while on biologics, may have three different types of "failure" to respond. Mechanistic failure occurs when the patient is not responding in spite of optimal drug trough concentrations. Antibody levels can be detectable or undetectable. This may occur because the disease is being driven by inflammatory mediators that are not blocked by this particular drug. In other words, the drug's mechanism of action is not working for this disease. These patients are unlikely to respond to other drugs within the same class and it is recommended that they switch to an out of class drug with a different mechanism of action.[13,14] The second type of failure is non-immune-mediated pharmacokinetic failure. This is when trough concentrations are subtherapeutic in the absence of anti-drug antibodies. The mechanism may be due to rapid drug clearance associate with a high inflammatory burden. The solution is escalation by increasing the dose or decreasing the interval between doses.[13,14] Finally, immune-mediated pharmacokinetic failure occurs in patients with low or undetectable trough concentrations with positive anti-drug antibodies. This type of drug failure results from formation of neutralizing anti-drug antibodies. The solution is to switch to a drug in class if there are high titer antibodies or if adding an immunomodulator or increasing the dose of the medication if low titer antibodies.[13,14]

Studies report optimal drug concentrations based on improved outcomes when reaching certain threshold drug levels. Feuerstein JD et al reported that the following trough concentrations should be targeted with anti-TNF agents. At least 5 mcg/mL for infliximab, at least 7.5 mcg/mL for adalimumab, and at least 20 mcg / mL for certolizumab. For vedolizumab, a biologic agent binding to alpha 4 beta 7 integrin used in both UC and CD, a concentration of 20 mcg/mL six week after vedolizumab infusions appeared to be associated with improved outcomes.[15] Ustekinumab is another biologic agent inhibiting the p40 subunit of interleukins 12 and 23, used in the treatment of UC and CD. One study reported the optimal level was greater than or equal to 26-week threshold trough concentration above 4.5 mcg/mL. In CD this was associated with endoscopic response and lower CRP levels.[16]

Biologics – Proactive Therapeutic Drug Monitoring

In adults with quiescent disease on anti-TNF therapy, the AGA makes no recommendations regarding the use of proactive drug monitoring.[1] However, many clinicians treating IBD support proactive therapeutic drug monitoring. Two randomized controlled trials evaluated proactive therapeutic drug monitoring. The first prospective study on proactive therapeutic drug monitoring was called TAXIT published in 2015.[17] It compared proactive drug monitoring to empiric dose escalation. They recruited 173 patients with moderate-severe Crohn's disease who were already on maintenance IFX. After recruited, they were optimized with adjusting doses of IFX to reach a predetermined target trough level. All patients underwent proactive drug monitoring. Following this phase patients were randomly assigned to receive empiric dose escalation based on their clinical symptoms or biochemical parameters versus proactive drug monitoring where they were dosed based on IFX trough levels. The primary endpoint was clinical and biochemical remission one year after optimization. During the first phase when they optimized all patients to a target trough level, the proportion of patient in clinical remission, increased by 23%. However, primary endpoint, the rate of clinical and biochemical remission between the two groups at 1 year after optimization, showed no significant difference. TAXIT was considered a negative study against proactive drug monitoring. However, flaws in the study design, including all patients were dose optimized before randomization and only followed for 1 year. Therefore, it was difficult to detect a significant difference in the primary endpoint. For the secondary endpoints, there were many differences noted. Fewer patients in the proactive TDM group needed rescue therapy and had undetectable troughs. There was also a nonsignificant trend toward few acute infusion reactions and while the cost between the two groups was similar – not increased in the proactive TDM group as may have been expected.

The second randomized prospective study on proactive TDM was called TAILORIX.[18] The primary aim was to determine whether proactive TDM produced higher rates of clinical and endoscopic remission compared to dose escalating based on symptoms alone. They recruited 122 patients with active luminal Crohn's disease who were biologic naïve. All patients received IFX for induction dosing and then were randomized to one of three groups. The control group received IFX dose escalation based on clinical symptoms. The other two groups received IFX at an escalated dose of 2.5mg/kg or 5mg/kg if they met certain clinical criteria in hierarchal order—symptomatic disease or biochemical evidence of disease followed by low trough levels. Because of this hierarchal design, only a small number of patients ended up receiving dose escalated in a proactive TDM manner, which reduced the power of the study. Unsurprisingly, the results showed no significant difference between the two groups. However, the study failed to meet its intended study aim of answering whether proactive TDM led to a difference in remission rates compared to dose escalation as there were so few patients who underwent proactive TDM. The study more directly compared dose escalation based on symptoms and biomarkers with dose escalation based on symptoms alone and found no difference. The lack of well-designed prospective studies with proactive TDM has hindered the AGA from recommending use.

A few well-designed retrospective studies examined proactive TDM. One study at al Beth Israel Deaconess Medical Center followed 264 patients with IBD on maintenance IFX therapy. Patients underwent proactive or reactive TDM based on their first IFX trough level. Patients were followed for a median of 2.4 years. Compared to reactive TDM, the proactive approach was independently associated with a reduced risk of treatment failure, IBD related surgery, and IBD related hospitalizations.[19] Another retrospective multicenter cohort study in 2018 followed 102 patients with Crohn's disease.[20] All patients initially underwent reactive TDM and then one group continued reactive TDM and the other group underwent proactive TDM. They found that the proactive TDM group was associated with fewer treatment failures and IBD hospitalizations.[20] Another retrospective published in 2014 examined the use of proactive TDM in IBD patients in clinical remission.[21] They followed 48 patients in clinical remission on IFX who underwent proactive TDM and identified a control group of 78 patients who achieved clinical remission on IFX but did not undergo proactive TDM. One of their endpoints was to see if proactive TDM was associated with a longer duration on IFX compared to the control group. They demonstrated that the proactive TDM group had a higher probability of remaining on IFX for the entire study period.

Although the AGA does not currently support proactive TDM due to lack of insufficient well-designed prospective studies, many IBD consensus groups, including the BRIDGe panel and Australian IBD consensus group support proactive TDM routinely at the end of induction during maintenance therapy, after a drug holiday, and before or after stopping an immunomodulator.[2] Limitations to adopting proactive TDM universally is cost and accessibility, as well as few well-designed prospective studies, and insufficient information on what adequate trough levels we should be targeting.

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