Therapeutic Drug Monitoring in Children and Young Adults With Inflammatory Bowel Disease: A Practical Approach

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Keywords
Inflammatory bowel disease, therapeutic drug monitoring, pharmacokinetics, immunogenicity, thiopurine metabolites, infliximab trough concentrations, infliximab levels

Abstract: Therapeutic drug monitoring (TDM) is the clinical practice of measuring drug concentrations or metabolites to attain a targeted concentration in a patient's bloodstream, thereby optimizing individual dosage regimens. With the well-established knowledge of the relationship of the genetic variability of thiopurine metabolism driven by the thiopurine *S*-methyltransferase pathway, and the recent data supporting pharmacokinetic variability and immunogenicity with anti–tumor necrosis factor (anti-TNF) therapies, TDM has emerged as a necessary mechanism to enhance drug efficacy. This article reviews data describing the relationship between drug concentrations and outcomes, including the achievement of a sustained and durable remission. The effect of antidrug antibodies on drug efficacy and toxicity is also examined. Furthermore, we describe different assays that are used for measuring these drug and antibody concentrations, including the advantages and pitfalls of these tools. An algorithm is proposed for clinical practitioners to utilize TDM in patients who are losing clinical response to anti-TNF therapy. A proactive, rather than reactive, approach to TDM of anti-TNF agents is supported by emerging data and will provide practitioners with the tools needed to optimally treat young inflammatory bowel disease patients.

Maximizing the efficacy of therapies for inflammatory bowel disease (IBD) while minimizing their toxicity remains the principal objective in developing management strategies for IBD patients. Recognition of the factors influencing therapeutic response allows clinicians to individualize dosing regimens to meet this objective. In order to optimize IBD therapy, it is critical that prescribers understand that standard dosing (ie, prescribing per the package insert or based on clinical trial data) is insufficient for most patients, given the interindividual variability relating to response and tolerability. With the well-established knowledge of the relationship of the genetic variability of thiopurine metabolism driven by the thiopurine *S*-methyltransferase (TPMT) pathway, and the increasing data supporting the pharmacokinetic variability and immunogenic-

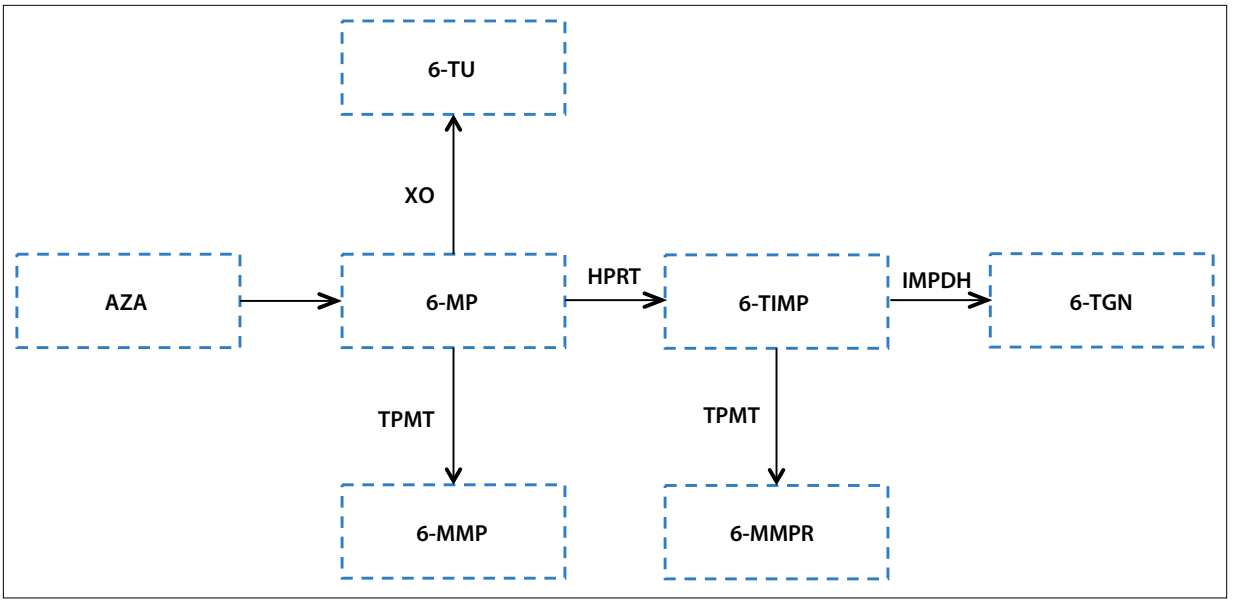

Figure 1. AZA/6-MP metabolism pathways.

AZA, azathioprine; HPRT, hypoxanthine phosphoribosyltransferase; IMPDH, inosine monophosphate dehydrogenase; 6-MMP, 6-methylmercaptopurine; 6-MMPR, 6-methylmercaptopurine ribonucleotide; 6-MP, 6-mercaptopurine; 6-TGN, 6-thioguanine nucleotide; 6-TIMP, 6-thioinosine monophosphate; TPMT, thiopurine *S*-methyltransferase; 6-TU, 6-thiouric acid; XO, xanthine oxidase.

ity with anti–tumor necrosis factor (anti-TNF) therapies, therapeutic drug monitoring (TDM) has emerged as a necessary mechanism to optimize drug efficacy with the goal of achieving a sustained and durable remission. Given the limited arsenal of medications available for young patients with IBD and the need for robust, long-term treatment strategies, TDM is an invaluable tool to help guide treatment decisions. This article reviews the historical and current utilization of TDM for treating young persons with IBD, as well as the accompanying challenges.

Thiopurine Monitoring

Efficacy and Drug Toxicity

TPMT levels and thiopurine metabolite measurements are currently used in clinical practice to manage patients receiving thiopurines, including 6-mercaptopurine and azathioprine. 6-Mercaptopurine and its prodrug, azathioprine, both undergo intestinal and hepatic metabolism by numerous enzymes, including hypoxanthine phosphoribosyltransferase, TPMT, xanthine oxidase, and inosine monophosphate dehydrogenase, to produce the active metabolites 6-thioguanine nucleotides (6-TGNs) and 6-methylmercaptopurine ribonucleotides (6-MMPRs)[1] (Figure 1). Through the study of these enzymes and metabolites in both IBD and oncology, the mechanisms of both drug efficacy and toxicity have been well established.

Obtaining a TPMT level prior to starting thiopurine therapy is common practice and the safest way to prescribe thiopurines, as this step determines the starting dose for an individual patient. For the 90% of patients with a normal TPMT level, the clinician may begin with standard dosing (azathioprine 2.5 mg/kg per day or 6-mercaptopurine 1.5 mg/kg per day). For the 10% of patients who are heterozygous for the *TPMT* gene, otherwise known as intermediate metabolizers, the clinician should prescribe half of the standard dose to minimize high 6-TGN levels and the risk of leukopenia. In the 1 of 300 patients who are homozygous for the *TPMT* gene, thiopurines are contraindicated, given the risk of life-threatening leukopenia.[2] TPMT-driven dosing negates the need for starting at a subtherapeutic dose, as knowledge of TPMT activity unblinds clinicians to the variability in metabolism, improving confidence in dosing selection.

TPMT drives initial dosing, yet the metabolites drive the efficacy and safety. In 1996, Cuffari and colleagues showed that higher 6-TGN metabolite concentrations correlated with clinical remission in pediatric Crohn's disease (CD) patients.[3] A further study in pediatric patients demonstrated that therapeutic response doubled in patients whose 6-TGN levels were greater than 235 pmol/8 × 10^8 red blood cells (RBCs; 78% vs 41%; P<.001).[4] That early study suggested that the odds of responding to thiopurines were 5 times higher in patients with 6-TGN levels greater than 235 pmol/8 × 10^8 RBCs than in patients with 6-TGN levels below this therapeutic threshold.[4] A 6-TGN level of 235 pmol/8 × 10^8 RBCs has been supported as a cutoff point in other pediatric and adult studies, and a meta-analysis reported that patients with 6-TGN concentrations above this threshold had a

3-fold increased odds of being in remission than patients below this threshold (62% vs 36%; pooled odds ratio [OR], 3.3; 95% CI, 1.7-6.3; $P<.001$).[5-8] The data suggest that in a patient not responding to standard thiopurine dosing, obtaining 6-TGN and 6-MMPR levels would be clinically useful. If 6-TGN levels are less than 235 pmol/8 × 10^8 RBCs, dose escalation is warranted; however, if 6-TGN levels are therapeutic (235-400 pmol/8 × 10^8 RBCs), switching classes to a nonthiopurine treatment would be indicated, given that the patient is not responding despite adequate drug concentrations.

Leukopenia is the most concerning toxicity associated with thiopurine use. This condition is almost always attributable to high 6-TGN levels. The patients most at risk of thiopurine-related myelosuppression are those who are homozygote deficient for the TPMT polymorphisms, as noted above. However, Colombel and colleagues reported that only 32% of cases of myelosuppression were secondary to lower TPMT activity, indicating that there are many other reasons for leukopenia, such as the effects of concomitant medications and secondary viral infections (eg, Epstein-Barr virus, cytomegalovirus, and parvovirus).[9] It is unclear what level of 6-TGN is considered too high, but a level greater than 400 pmol/8 × 10^8 RBCs has been suggested as the ceiling that clinicians should aim to avoid.[10]

Hepatotoxicity is another concern with the use of thiopurines, with some studies associating it with high 6-MMPR concentrations of greater than 5700 pmol/8 × 10^8 RBCs ($P<.05$).[4] Clinically, if a patient has a therapeutic 6-TGN level with a 6-MMPR level of greater than 5700 pmol/8 × 10^8 RBCs and normal liver enzyme levels, more frequent monitoring of liver enzymes is required rather than a reflexive dose adjustment. If, however, a patient has both a high 6-TGN level (>400 pmol/8 × 10^8 RBCs) and a high 6-MMPR level (>5700 pmol/8 × 10^8 RBCs), then dose de-escalation is warranted to minimize the risk of leukopenia and hepatotoxicity.

Perhaps the most important application of high 6-MMPR levels is in patients who also have a low 6-TGN level, with subsequent dose escalation resulting in decreasing 6-TGNs and increasing 6-MMPRs.[11] This group has been defined as being thiopurine resistant, or 6-MMPR preferential metabolizers, and such patients would benefit from changing their therapy to another class of medications, such as methotrexate or anti-TNF therapy. The proposed use of allopurinol to improve the thiopurine metabolic profile with higher 6-TGN levels and lower 6-MMPR levels may carry excessive toxicity risks with relation to leukopenia.[12]

Thiopurine drug monitoring is necessary to explain drug response and toxicity. This concept of measuring drug concentrations set the stage for other medications used in IBD, most notably the anti-TNF agents. We now have the tools to optimize therapies, and in this era of TDM, a patient should not be considered a nonresponder until a drug's concentration has been measured and adjusted accordingly.

Anti–Tumor Necrosis Factor Monitoring

Despite anti-TNF therapies being approved for use in adult IBD patients since 1998 and in pediatric patients since 2006, only recently has the link been made between the durability of these therapies and their pharmacokinetic profiles. The majority of the studies performed to date have been with infliximab (Remicade, Janssen Biotech), with emerging evidence for the other anti-TNF agents, including certolizumab pegol (Cimzia, UCB) and adalimumab (Humira, AbbVie).

Primary response to infliximab induction is successful in 75% to 90% of pediatric IBD patients, yet the maintenance of a sustained and durable remission with infliximab has become an important clinical challenge in the management of both pediatric and adult IBD patients.[13,14] In the REACH trial (Randomized, Multicenter, Open-Label Study to Evaluate the Safety and Efficacy of Anti-TNF-α Chimeric Monoclonal Antibody in Pediatric Subjects With Moderate to Severe Crohn's Disease), only 60% of pediatric CD patients who responded to induction were in remission at 1 year, and half of these patients required dose modification after losing response.[13] In a meta-analysis of adult IBD patients taking infliximab, 23% to 46% required dose escalation, and 5% to 13% discontinued the agent at 1 year.[15] Given that the goal of IBD management is to use these therapies for a long period of time, TDM affords clinicians the opportunity to understand the etiology of primary and secondary nonresponse. Herein, we describe the advances that have been made since the original description of the link between infliximab efficacy, drug concentrations, and immunogenicity.

Anti–Tumor Necrosis Factor Drug Concentrations and Outcomes

In 2003, Baert and colleagues initially found that higher serum infliximab concentrations correlated with a longer duration of response in CD patients.[16] In 2006, Maser and colleagues reported that detectable serum infliximab concentrations were associated with a higher rate of clinical remission, lower C-reactive protein (CRP) values, and endoscopic improvement.[17] Further studies reaffirmed that detectable infliximab concentrations were predictive of a sustained response in CD patients.[18] In ulcerative colitis (UC), the data are as robust, with detectable infliximab concentrations associated with significantly higher remission rates, endoscopic improvement, and a striking decrease in the risk of colectomy (55% vs 7%; OR, 9.3; 95% CI, 2.9-29.9; $P<.001$).[19] In the post hoc analysis of the ACT (Active Ulcerative Colitis Trial) 1 and 2 stud-

ies, higher infliximab concentrations in UC patients were associated with an increased likelihood of achieving clinical remission and mucosal healing with increasing quartiles of infliximab levels.[20] Patients with drug levels in the third or fourth quartile had remission rates at week 30 that were close to 60%, compared with 25% in patients in the second quartile.

As with infliximab, higher plasma concentrations of certolizumab pegol in CD patients have been associated with endoscopic response and remission,[21] and Roblin and colleagues found that higher adalimumab concentrations correspond to clinical remission and mucosal healing.[22] There have been attempts to determine a minimal quantitative infliximab trough concentration that is most associated with improved outcomes. Murthy and colleagues showed that in UC, an infliximab concentration of greater than 2 µg/mL was associated with a higher rate of corticosteroid-free remission, compared with a trough concentration of less than 2 µg/mL (69% vs 16%; $P<.001$).[23] A trough concentration of greater than 3 µg/mL during maintenance therapy, as measured by the now commercially available homogeneous mobility shift assay (HMSA), has been shown by Feagan and colleagues to be independently associated with a lower CRP level and has been proposed as a cutoff value to maximize the clinical efficacy of infliximab.[24] It is important to point out that until recently, all studies on infliximab concentrations and efficacy have been reported using enzyme-linked immunosorbent assays (ELISAs) or ELISA-based tests. The importance of this distinction is addressed in the section below on assays.

Karmiris and colleagues suggested a therapeutic threshold of greater than 8 mg/mL for adalimumab concentrations.[25] Velayos and colleagues found that concentrations of greater than 5 µg/mL were related to decreased CRP levels,[26] and Yarur and colleagues confirmed this association.[27] In the post hoc analysis of the WELCOME (26-Week Open-Label Trial Evaluating the Clinical Benefit and Tolerability of Certolizumab Pegol Induction and Maintenance in Patients Suffering From Crohn's Disease With Prior Loss of Response or Intolerance to Infliximab) trial, in which 203 patients received induction with certolizumab pegol, remission rates were higher among patients whose certolizumab pegol concentration fell within the 2 highest quartiles (27.5-33.8 µg/mL and ≥33.8 µg/mL) during induction at weeks 0, 2, 4, and 6; thus, a certolizumab pegol concentration of greater than 27.5 µg/mL has been proposed for clinical use.[28]

Antidrug Antibodies: Influence on Efficacy and Toxicity

Despite a high primary response rate with anti-TNF agents, two-thirds of patients who lose response do so within the first year.[15] The loss of response to anti-TNF agents is most often due to an individual's response to the agent's pharmacokinetic profile and is driven by drug clearance. Additionally, the development of antidrug antibodies (ADAs), otherwise referred to as immunogenicity, remains a significant driver of loss of response. The presence of ADAs increases the clearance of the drug, meaning that patients with ADAs clear the drug faster, resulting in lower drug concentrations. This results in a shorter duration of response.[16,17,21,29-33]

In addition to the effect that ADAs have on efficacy, their presence also influences toxicity, with the example of anti–infliximab antibodies (ATIs) being associated with infusion reactions.[30] With the self-injectable anti-TNF therapies, the effect of ADAs is linked to drug clearance and efficacy. Recent data demonstrate that ATIs may be transient. Vande Casteele and colleagues retrospectively found that ATIs disappeared over time in 28% of patients, although ATIs were sustained in the majority (72%) of patients with ATI positivity.[33] It still remains unknown whether low concentrations of ATIs may be overcome by infliximab dose escalation, whereas higher ATI concentrations are less likely to be reversed, and in such patients, their therapy should be changed to another anti-TNF agent.

The presence of ADAs is also very important in the setting of reintroduction of anti-TNF therapies after a prolonged interruption (drug holiday). Baert and colleagues found that the presence of ATIs after the first reinduction dose of infliximab, measured at the time of the second dose given 2 weeks later, was associated with lower response rates to reinduction and higher rates of infusion reactions.[34] The data suggest that if a patient has not been receiving infliximab for 6 months or more, it is important to know the patient's ATI status prior to administering the second induction dose. Whether a patient should be treated with a 0-, 2-, and 6-week reinduction regimen or forego reinduction and resume with an every-8-week dosing interval remains unclear.

All attempts should be made to reduce the likelihood of ADA formation, given the strong association with loss of drug efficacy and toxicity. Various strategies have been introduced to do so, such as concomitant immunomodulator use and optimizing drug concentrations throughout the dosing interval to ensure that the patient is never exposed to subtherapeutic concentrations. It should be noted that non-chimeric anti-TNF therapies have the same issue with ADA formation as chimeric ones.[35] Moreover, it has been suggested that subcutaneously administered therapies are associated with more ADA formation than therapies administered intravenously. The reported rates of ADA formation, both in trials and in data reported in package inserts, are entirely dependent on the specific assay used to measure ADAs.

Aside from ADAs, other factors that influence drug clearance of anti-TNF agents have been described. These include low serum albumin concentrations, high baseline

CRP levels, large body size, male sex, and a high degree of systemic inflammation.[32] Additionally, emerging evidence suggests that severe UC patients have very rapid clearance of infliximab, decreasing the half-life by 10-fold, as well as rapid loss of infliximab via the very inflamed colon, with measurable fecal infliximab concentrations.[36,37] Using infliximab at an increased dose of 10 mg/kg for induction in a hospitalized UC patient with low albumin and high CRP levels warrants formal evaluation.

Use of Concomitant Immunomodulators: Influence on Antidrug Antibodies and Efficacy

In the ACCENT (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen) I trial, concomitant immunomodulator use with infliximab was associated with lower rates of ATI formation.[38] In the CD prospective cohort described by Baert and colleagues, patients who received concomitant immunosuppressive therapy were found to have higher infliximab concentrations and a lower incidence of ATI formation than those not receiving immunosuppressive agents (43% vs 75%; $P<.01$).[16] A logistic regression analysis further demonstrated that taking concomitant immunosuppressive agents was the only variable of significance ($P<.001$) that was predictive of infliximab concentrations.[16] The SONIC (Study of Biologic and Immunomodulator-Naive Patients in Crohn's Disease) trial demonstrated that combination therapy with infliximab and azathioprine is superior to infliximab monotherapy in achieving clinical remission and mucosal healing.[31] This is likely due to less formation of antibodies and higher trough levels associated with combination therapy, rather than to having 2 immunomodulators on board. Patients receiving adalimumab in combination with an immunomodulator have likewise been found to have higher drug concentrations than those receiving monotherapy.[27]

Ben-Horin and colleagues demonstrated in 5 patients who had lost response to infliximab monotherapy, in the face of low drug concentrations and ATIs, that the addition of an immunomodulator restored clinical response by increasing infliximab drug concentration and decreasing ATIs.[39] Ong and colleagues likewise showed that the addition of a thiopurine in 5 patients losing response to anti-TNF monotherapy was an efficacious strategy to recapture response.[40] These small studies suggest that concomitant immunomodulator use may not only decrease immunogenicity preemptively, as suggested by the SONIC trial, but may also be used to recapture response in patients with low drug concentrations. This concept merits further exploration and validation.

The efficacy of combining an anti-TNF agent with methotrexate has been examined as well. The COMMIT trial (Combination of Maintenance Methotrexate-Infliximab Trial) showed that patients receiving combination therapy with infliximab and 25 mg of methotrexate administered subcutaneously were significantly less likely to develop ATIs and had higher infliximab concentrations than patients receiving infliximab alone; however, no clear benefit was found in inducing and maintaining clinical remission.[41] In the rheumatoid arthritis literature, a dose as low as 7.5 mg weekly was associated with lower rates of ATI development.[42] Vahabnezhad and colleagues, however, found no clinical benefit in infliximab durability or efficacy by using concomitant low-dose oral methotrexate (<10 mg/week) in pediatric IBD patients.[43] It may be that a higher dose of oral methotrexate is needed to influence immunogenicity. A group from Germany found that concomitant use of methotrexate and infliximab had a promising effect in the treatment of adult refractory CD patients, using a methotrexate dose of 20 mg weekly administered both parenterally and orally.[44] In pediatric patients, particularly in males under the age of 21 years, the substitution of methotrexate for thiopurines may provide a safety advantage, given the lack of association between hepatosplenic T-cell lymphoma and combination therapy with infliximab and methotrexate in this age group. Long-term exposure data are needed to confirm this improved safety profile.

Decision Making Driven by Therapeutic Drug Monitoring

In a patient who has lost response to infliximab, a commonly practiced salvage therapy is empiric dose intensification of infliximab or switching to another agent within or outside the anti-TNF class. However, the efficacy of switching to other agents without knowing the mechanism for loss of response is less than ideal, as switching can rapidly exhaust available treatment options. Using TDM to guide treatment decisions based on the reason for loss of response is a superior option, and this concept has been demonstrated in numerous studies.

Both the placebo-controlled GAIN (Gauging Adalimumab Efficacy in Infliximab Nonresponders) study[45] and the open-label WELCOME study (with certolizumab pegol)[46] took CD patients who had lost response to infliximab and had their therapy switched to another anti-TNF agent blindly without prior knowledge of infliximab concentration or ATI status. This resulted in a week 4 remission rate of 21% with adalimumab and a week 6 remission rate of 39% with certolizumab pegol. One may propose that efficacy rates could have been higher by optimizing infliximab dosing, given that the reason for infliximab failure was most likely low drug concentrations rather than ADA-driven loss of response.

Uncontrolled clinical studies do support this notion in both UC and CD patients. In patients with loss of clinical response and a combination of low infliximab concentrations and undetectable ATIs, infliximab dose intensification is indicated as the preferred strategy. Ben-Horin

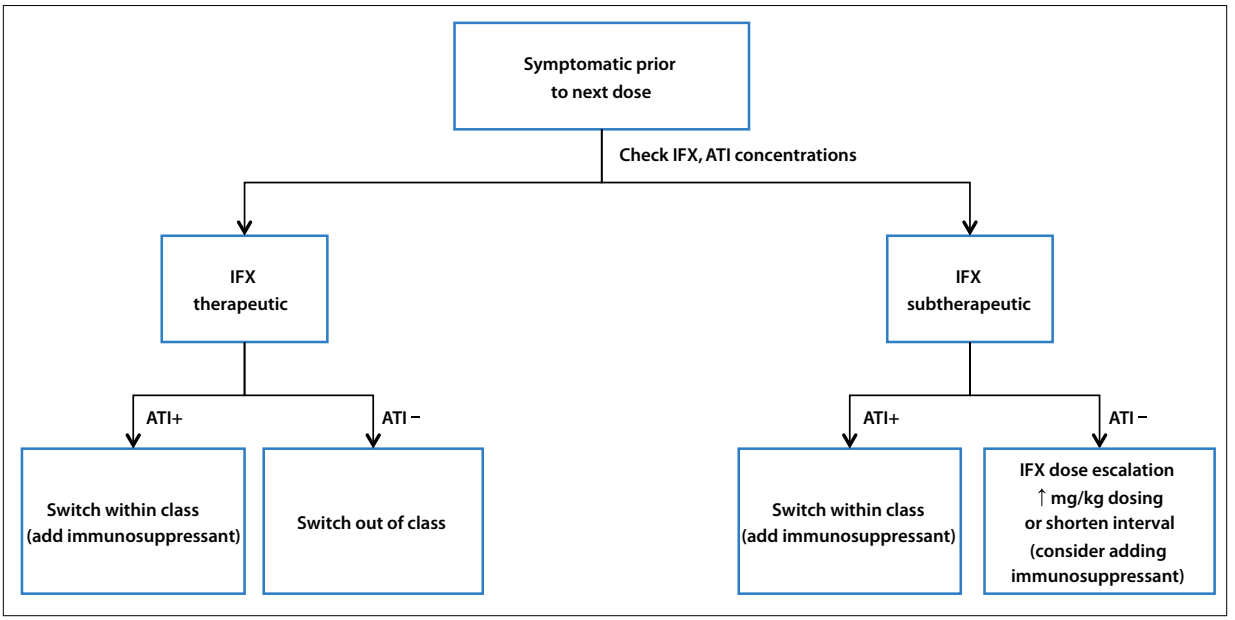

Figure 2. Utilizing therapeutic drug monitoring with IFX therapy.

ATI, anti–infliximab antibody; IFX, infliximab.

and Chowers found that of the patients losing response to infliximab and requiring dose intensification, 50% to 70% had regained response at 12 months, asserting the success of recapturing response with dose escalation.[15] Afif and colleagues performed a retrospective study of 155 patients receiving infliximab and noted that increasing the infliximab dose resulted in a clinical response in 86% of patients, whereas changing to another anti-TNF agent resulted in a mere 33% response rate.[47] In a multicenter retrospective study of 168 CD patients who had lost response to the standard infliximab dose, Katz and colleagues found that dose intensification beyond the standard 5 mg/kg every 8 weeks of infliximab led to sustained regained response in 47% of patients; in addition, the researchers found that both dose and frequency escalation (to 10 mg/kg every 8 weeks and 5 mg/kg every 4 weeks) were equally as efficacious.[48] The cost and inconvenience of having more frequent visits for infusions need to be an important part of the decision as to whether or not to escalate the dose or frequency. Afif and colleagues also showed that in those patients who had ATIs and undetectable infliximab concentrations, switching to another anti-TNF agent led to partial clinical response in 92%, whereas only 17% (1 of 6) of the patients who had doses escalated in the face of ATIs had an improvement in response (P<.004).[47] This revisits the question of whether ADAs may be overcome by dose escalation. It should be noted that this was successful in only 1 patient and that in further follow-up, the patient required switching to another anti-TNF agent, as the response was not sustained. Thus, assessment of infliximab and ATI concentrations is clinically useful to optimize patient treatment regimens (Figure 2). More recently, utilizing TDM to optimize treatment has been shown to be not only more efficacious but also more cost-effective, compared with using empiric dose escalation.[49,50]

Understanding the Different Assays Used to Measure Drug Concentrations and Antidrug Antibodies

Several methods are available for measuring concentrations of anti-TNF agents and ADAs, so comparing results from different assays should be done with caution. Drug concentrations are generally detected with equal sensitivity with all assay types, yet the detection and accurate quantification of ADAs have been challenging. First-generation assays, such as ELISAs, have less clinical utility, given their insensitivity for measuring ADAs. Using the ELISA method, a serum anti-TNF drug competes with the ADA detection moiety, so when the drug is detected in the sample, ADA results are reported as inconclusive.[51] Radioimmunoassay tests are sensitive and specific for drug and ADA detection, yet disadvantages include the complexity of the tests, prolonged incubation time, expense, and handling of radioactive materials.[51,52] HMSA, using high-performance liquid chromatography, has the advantage of being drug tolerant and highly accurate in detecting both the drug and ADAs in the same sample. HMSA separates and quantifies the drug and antibody concentrations independently, making it possible to detect ADAs in the presence of the anti-TNF drug. Standardization between these assays is not present, causing difficulty in interpreting results between different assay types. ELISAs and ELISA-like tests (LabCorp, Esoterix) as well as HMSA (Prometheus Laboratories) are currently

commercially available for the evaluation of infliximab. HMSA is now also available for evaluation of adalimumab concentrations and anti–adalimumab antibody titers.

Future Direction of Therapeutic Drug Monitoring

Given the literature supporting the role of TDM, prospective trials using TDM-based dose adjustment have been performed recently. The TAXIT (Trough Level Adapted Infliximab Treatment) study optimized the infliximab dose in IBD patients who were already in remission receiving maintenance infliximab therapy, to obtain an infliximab concentration between 3 and 7 μg/mL.[53] CRP levels and disease activity indices significantly improved with dose optimization in the patients with CD, but not those with UC. In the second part of the TAXIT study, the patients were randomized to clinically based vs infliximab concentration–based dose adjustments. Although the proportion of patients achieving clinical and biologic remission at the primary endpoint was the same in both groups (69% vs 72%; *P*=.7), those patients whose doses were adjusted based on their infliximab concentrations, regardless of whether they were in remission clinically, had a more durable remission state, less ATI formation, and higher infliximab concentrations than those treated with clinically based dose adjustments.[54] The study does suggest that occasional monitoring and dose optimization may be prudent, even in patients who report that they are doing well clinically on maintenance therapy.

Perhaps the most important utilization of TDM is in preventing loss of response, rather than waiting for a patient to become a nonresponder. This can be accomplished by proactively dose adjusting early in the treatment course. Researchers have attempted to determine whether a drug concentration obtained early in maintenance therapy is a predictor of a more durable response. Bortlik and colleagues found that, on retrospective evaluation of 84 CD patients, an infliximab cutoff value of greater than 3 μg/mL at either the week 14 or the week 22 dose was predictive of a sustained response.[18] Vande Casteele and colleagues found that low infliximab concentrations at 14 weeks (<2.2 μg/mL) in 90 CD and UC patients predicted infliximab discontinuation due to persistent loss of response and were associated with an increased incidence of ATIs.[33] In a recent post hoc analysis of ACCENT I, patients with postinduction week 14 infliximab concentrations of 3.5 μg/mL or greater and a 60% or greater decrease in CRP levels from baseline were significantly associated with durable sustained response at week 54.[55] Using a cohort of 50 pediatric IBD patients, Singh and colleagues were the first to prospectively determine the optimal cutoff point for a week 14 infliximab trough concentration in predicting 1-year durable remission.[56] In this study, a concentration of at least 5.5 μg/mL was described as optimal (*P*=.01).[56] The next step is to determine whether there are other variables, other than CRP levels and postinduction drug concentrations, that predict 1-year outcomes. There is a need for prospective studies in which patients receive proactive dose escalation in the postinduction period, with results compared with standard clinically based dose escalation.

Conclusion

The clinical value of TDM is increasingly being recognized, with the growing body of evidence linking serum anti-TNF drug and ADA concentrations to clinical outcomes in IBD. The knowledge of these results provides insight into the etiology of loss of response and enables therapy to be optimized for an individual patient. As more is understood regarding the pharmacokinetics of anti-TNF therapies, new algorithms for their use will be developed to aid in the achievement of a sustained and durable remission. The concept of dose optimization was initially used with thiopurines over a decade ago, and the knowledge gained is now applied to anti-TNF therapies, providing clinicians with the tools required to improve IBD management. Issues of clearance and immunogenicity are not unique to anti-TNF therapies, and these challenges will be applicable to all biologic agents used in IBD patients. The era of personalized medicine has arrived, and TDM allows for optimized, individualized dosing and improved care for IBD patients of all ages.

Dr Singh has received research support from Janssen. Dr Dubinsky has been a consultant for Janssen, Pfizer, Bristol-Myers Squibb, UCB, Abbott, Shire, Prometheus, and Takeda, and she has received research support from Janssen.

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