A Personalized Approach to Managing Inflammatory Bowel Disease

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Abstract: The management of inflammatory bowel disease (IBD) requires a personalized approach to treat what is a heterogeneous group of patients with inherently variable disease courses. In its current state, personalized care of the IBD patient involves identifying patients at high risk for rapid progression to complications, selecting the most appropriate therapy for a given patient, using therapeutic drug monitoring, and achieving the individualized goal that is most appropriate for that patient. The growing body of research in this area allows clinicians to better predict outcomes for individual patients. Some paradigms, especially within the realm of therapeutic drug monitoring, have begun to change as therapy is targeted to individual patient results and goals. Future personalized medical decisions may allow specific therapeutic plans to draw on serologic, genetic, and microbial data for Crohn’s disease and ulcerative colitis patients.

Care of the inflammatory bowel disease (IBD) patient presents unique challenges, as decisions regarding therapy must take into account numerous distinct characteristics of each patient. Beyond the dichotomy between Crohn’s disease (CD) and ulcerative colitis (UC), which may be difficult to ascertain in some patients, a number of distinct phenotypes exist within these diseases. IBD can be categorized by existing severity, location and extent, and potential for complications. It may be further categorized according to responsiveness to medical therapy. A number of individualized markers of disease, however, may allow for better prediction of response to therapy and disease course. Decisions for therapy must also be tailored to the comorbidities or risks of an individual patient, such as the risk of hepatosplenic T-cell lymphoma among men younger than 35 years. As such, IBD constitutes an opportunity for personalized medicine, and strategies should be tailored to maximize the success of the current treatment, minimize loss of response to therapy or relapses in the future, and address the risks associated with specific medications for given patients.

Keywords
Inflammatory bowel disease, ulcerative colitis, Crohn’s disease, personalized medicine, therapeutic drug monitoring, biomarkers, serologic markers
Therapeutic Drug Monitoring in Inflammatory Bowel Disease

Although a clinician might have previously considered starting a medication at a standard dose and titrating based upon clinical response, therapeutic drug monitoring (TDM) allows for more accurate adjustment of drug levels in an individual patient. IBD management leads the field of TDM. Clinicians caring for IBD patients have a variety of tests available that have been shown to optimize the efficacy of drugs and minimize toxicity.

TDM is important in the management of patients on thiopurines such as azathioprine (AZA) and 6-mercaptopurine (6-MP) to limit side effects such as myelosuppression and hepatotoxicity. Prior to starting thiopurine therapy, an assay should be conducted of the enzymatic activity of thiopurine methyltransferase (TPMT), a critical enzyme in the degradative pathway of 6-MP/AZA, as this type of assay has been reported to better predict myelosuppression than assays of genotype. In fact, the correlation of genotype with enzymatic activity has been reported to be as low as 65%. An exception to this paradigm would be a patient who recently received a transfusion of red blood cells (RBCs), in which case TPMT genotype would yield more accurate results. Intermediate TPMT enzymatic activity is generally associated with increased efficacy and typically requires lower doses because patients generate higher levels of the active metabolite thioguanine.

Following the initiation of therapy, measurement of the thiopurine metabolites 6-thioguanine nucleotide (6-TGN) and 6-methylmercaptopurine (6-MMP) is useful in multiple ways. Many studies have demonstrated that 6-TGN levels greater than 230 pmol/8 × 10^8 RBCs are associated with increased efficacy. However, supratherapeutic levels, generally above 400 pmol/8 × 10^8 RBCs, are associated with an increased risk of myelosuppression, which is not necessary for efficacy. 6-MMP can be measured to predict the risk of hepatotoxicity; levels greater than 5700 pmol/8 × 10^8 RBCs carry a 3-fold risk of hepatotoxicity. Importantly, most patients with 6-MMP levels above 5700 pmol/8 × 10^8 RBCs do not have hepatotoxicity; thus, the metabolites have to be viewed in the context of the particular patient.

There are other situations in which TDM for 6-MP metabolites is helpful. Among nonresponders to thiopurines, dose escalation resulted in hepatotoxicity for 24% of patients, with median 6-MMP ribonucleotide levels greater than 12,000 pmol/8 × 10^8 RBCs and median 6-TGN levels remaining subtherapeutic. In such cases, combining a reduced dose of AZA with allopurinol 100 mg will preferentially shunt 6-MP metabolism toward 6-TGNs. Recent studies have suggested that patients exhibiting 6-MMP:6-TGN ratios of 12:1 to 20:1 do well with the addition of allopurinol. These studies have largely been performed in patients on thiopurine monotherapy. For patients on combination therapy of thiopurines and biologics, the question becomes whether therapeutic 6-TGN levels are necessary for increasing trough levels of biologics. A recent study by Yarur and colleagues suggested that for patients on combination therapy of thiopurines and infliximab (Remicade, Janssen), the threshold for increased levels of infliximab was seen with 6-TGN levels above 125 pmol/8 × 10^8 RBCs, thus obviating the need for therapeutic levels of 6-TGNs.

For anti–tumor necrosis factor (TNF) agents, numerous patient-specific factors, including body mass, concomitant use of immunomodulators, antidrug antibodies (ADAs), inflammatory markers, and albumin, may affect drug levels. Ideally, these factors should be taken into account to decide the starting dose of anti-TNF agents, as is done with TPMT testing. For example, initiation of weekly adalimumab (Humira, AbbVie) provided significantly higher remission rates than standard biweekly adalimumab dosing among CD patients with an elevated baseline C-reactive protein (CRP), but did not result in significantly higher rates of remission in those with lower CRP. Similarly, an elevated baseline CRP also predicted response to high-dose infliximab.

TDM has been best studied for infliximab and adalimumab, and includes the measurement of both drug and antibodies to infliximab (ATIs) or antibodies to adalimumab (ATAs). Higher clinical remission rates are seen in patients with detectable trough infliximab levels. Studies have identified concentrations predictive of response ranging from 1.4 to 12.0 μg/mL (Table). For adalimumab, cutoffs predictive of remission, as measured by CRP, range from 5.0 to 5.9 μg/mL, or from 4.9 to 7.5 μg/mL when assessing mucosal healing. Histologic remission, however, may require even higher levels of adalimumab. In the CLASSIC (Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn’s Disease) I and II studies, a wide variation of adalimumab levels was seen among individual patients, with substantial overlap noted between responders and nonresponders. The variation in cutoff values reported and the variation in the ability of levels to predict response may reflect the heterogeneity in defining response and the inherently flawed dimension of clinical response as distinct from endoscopic and histologic response. The timing of drug level measurement may also be critical to the ability of a drug level to predict response, as studies have suggested that trough concentrations more accurately predict clinical remission than peak concentrations. A recent abstract suggests that levels of infliximab
Table. Characterization of Anti-TNF Levels and Response Outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Therapeutic Level</th>
<th>Time of Measurement</th>
<th>Test Type</th>
<th>Definition of Response Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afif et al(^1)(^6)</td>
<td>Infliximab</td>
<td>Cutoff: 1.4 μg/mL</td>
<td>Trough</td>
<td>ELISA</td>
<td>Clinical response: cessation of diarrhea, abdominal cramping, or fistula closure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cutoff: 12.0 μg/mL</td>
<td>4 weeks after infusion</td>
<td>ELISA</td>
<td>Clinical response: cessation of diarrhea, abdominal cramping, or fistula closure</td>
</tr>
<tr>
<td>Bortlik et al(^1)(^7)</td>
<td>Infliximab</td>
<td>Cutoff: 3.0 μg/mL</td>
<td>Trough</td>
<td>ELISA</td>
<td>Sustained clinical response: no need for surgery, no new immunomodulator, no corticosteroids, and no dose increase of infliximab</td>
</tr>
<tr>
<td>Van Moerkercke et al(^1)(^8)</td>
<td>Infliximab</td>
<td>Median: 5.77 μg/mL</td>
<td>Trough</td>
<td>ELISA</td>
<td>Mucosal healing: Complete healing: disappearance of all lesions Partial healing: clear endoscopic improvement</td>
</tr>
<tr>
<td>Baert et al(^1)(^9)</td>
<td>Infliximab</td>
<td>Cutoff: 12.0 μg/mL</td>
<td>4 weeks after infusion</td>
<td>ELISA</td>
<td>Duration of clinical response</td>
</tr>
<tr>
<td>Papamichael et al(^1)(^7)</td>
<td>Infliximab</td>
<td>Cutoff: 22.5 μg/mL</td>
<td>Week 2</td>
<td>ELISA</td>
<td>Short-term mucosal healing (Mayo 0-1 endoscopic subscore) after induction</td>
</tr>
<tr>
<td>Imaeda et al(^1)(^0)</td>
<td>Adalimumab</td>
<td>Cutoff: 5.9 μg/mL</td>
<td>Trough</td>
<td>ELISA</td>
<td>CRP level ≤0.3 mg/dL</td>
</tr>
<tr>
<td>Yarur et al(^1)(^1)</td>
<td>Adalimumab</td>
<td>Cutoff: 5.0 μg/mL</td>
<td>Random</td>
<td>HMSA</td>
<td>CRP elevation</td>
</tr>
<tr>
<td>Roblin et al(^1)(^2)</td>
<td>Adalimumab</td>
<td>Cutoff: 4.85 μg/mL</td>
<td>Trough</td>
<td>ELISA</td>
<td>Clinical remission: UC: Mayo score &lt;3 CD: CDAI &lt;150</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cutoff: 4.9 μg/mL</td>
<td>Trough</td>
<td>ELISA</td>
<td>Mucosal healing: UC: Mayo endoscopic subscore 0-1 CD: disappearance of all ileocolonic ulcerations</td>
</tr>
<tr>
<td>Yarur et al(^1)(^3)</td>
<td>Adalimumab</td>
<td>Cutoff: 7.5 μg/mL</td>
<td>Trough</td>
<td>HMSA</td>
<td>Endoscopic healing: lack of inflammatory findings in intestinal mucosa</td>
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<tr>
<td></td>
<td></td>
<td>Cutoff: 7.8 μg/mL</td>
<td>Trough</td>
<td>HMSA</td>
<td>Histologic remission: lack of histologic inflammation on biopsies</td>
</tr>
</tbody>
</table>

CD, Crohn’s disease; CDAI, Crohn’s Disease Activity Index; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; HMSA, homogenous mobility shift assay; TNF, tumor necrosis factor; UC, ulcerative colitis.

measured at week 4 can be used to predict trough levels.\(^2\)\(^6\)

The implication is that a clinician can see the level early enough to make dose adjustments rather than wait for a trough. As a corollary, high infliximab concentrations (>22.5 μg/mL) measured at week 2 of induction may predict short-term mucosal healing.\(^2\)\(^7\) Thus, in general, higher levels are needed to induce mucosal healing, and it may be possible to measure these levels early during induction, rather than wait for loss of response.

What has been learned about TDM for anti-TNF agents may also apply to other monoclonal antibody–based biologic therapies for IBD. Studies of vedolizumab (Entyvio, Takeda) have shown that higher trough levels resulted in increased rates of clinical response and remission in UC and CD patients.\(^2\)\(^8\),\(^2\)\(^9\) Although an assay is not currently commercially available for measuring vedolizumab in serum, future care of the IBD patient treated with vedolizumab may include monitoring drug levels to optimize response.

Low levels of anti-TNF agents are associated with developing ADAs and preceded the formation of ATIs and ATAs.\(^3\)\(^0\),\(^3\)\(^1\) Once they are generated, however, ATIs and ATAs increase drug clearance of anti-TNF agents and are associated with lower serum drug levels as well as active disease and loss of response.\(^3\)\(^2\),\(^3\)\(^3\) It therefore becomes imperative to prevent patients from developing ATIs or ATAs. This can be accomplished by proactive, rather than reactive, drug monitoring. Using this strategy, patients
were shown to have a greater probability of remaining on infliximab than patients receiving standard of care. Measurement of trough levels as early as week 14 of therapy has also been shown to predict long-term outcomes. Together, these studies suggest that proactive, early assessment of trough levels of biologic therapies will allow for dose optimization and may maximize the likelihood of persistent remission for an individual patient. A summary of this strategy is presented in the Figure.

With knowledge of an individual patient’s serum levels and ATI/ATA status, a clinician may guide therapeutic decisions accordingly. In the case of subtherapeutic serum drug levels and the absence of ATIs or ATAs, experts have advocated a strategy of intensification, in which dosage is increased or the intervals between administrations are decreased. According to this schema, those with detectable ATIs or ATAs should be switched to an alternate anti-TNF agent because most patients with ADAs do not respond to dose escalation. Vande Casteele and colleagues, however, have shown that ATIs may be transient, which was the case in 28% of their study cohort. Some data have even suggested that the initiation of an immunomodulator or the intensification of therapy may result in the suppression of ATIs.

For patients with therapeutic levels of drug and no ATIs/ATAs but without clinical response, switching classes of medications may be reasonable (although this should be considered carefully). Intensification may also be successful in these cases. In fact, 70% of patients with therapeutic drug levels had a clinical response to dose intensification. This may reflect the variability among patients with respect to their own therapeutic levels. A lack of response despite therapeutic serum levels may be due to a high inflammatory burden within the gastrointestinal tract, as higher anti-TNF concentrations in tissue may be necessary in the face of greater inflammation at the tissue level.

Nonetheless, intensification with the use of TDM has resulted in significantly higher rates of clinical response, fewer hospitalizations, and fewer flares as
compared to dosage adjustments based upon clinical assessment alone. In summary, TDM can be valuable for optimizing the most effective medications and allows individualization of doses.

**Traditionally Used Serologies and Emerging Biomarkers for Guiding Management in Inflammatory Bowel Disease**

Although serologies have long been used to aid in the diagnosis of UC and CD, they and other biomarkers may also be of great utility in predicting disease outcomes for an individual patient. A recent study found that anti-**Saccharomyces cerevisiae** antibody (ASCA) immunoglobulin A and G (IgA and IgG) and the flagellin antibodies anti-A4-Fla2 and anti-FlaX predict complicated CD years before diagnosis. Dubinsky and colleagues also demonstrated an increased frequency of internal penetrating and stricturing disease and the need for surgery with increasing levels of ASCA, anti-outer membrane protein C (anti-OmpC), and anti-CBir1 flagellin in a prospectively ascertained cohort of pediatric patients. Serologies may also predict postoperative recurrence of CD. For example, after measuring antineutrophil cytoplasmic antibody (ANCA), ASCA, anti-OmpC, anti-CBir1, anti-A4-Fla2, and anti-FlaX, a positive anti-FlaX or a negative ANCA predicted higher rates of postoperative recurrence of CD. Whereas serologies may be helpful to predict phenotype in CD patients, they are generally not helpful in predicting response to anti-TNF agents. Recent proteomic analysis of patient serum has suggested that numerous additional targets such as apolipoprotein A1, apolipoprotein E, complement C4B, plasminogen, serotransferrin, beta-2 glycoprotein 1, and clusterin are upregulated in patients with limited response to infliximab as compared to patients in remission. Although not currently standard practice, knowledge of a patient’s serology results may guide medication choices or prompt a clinician to pursue a more aggressive strategy.

**Genetic Testing in Inflammatory Bowel Disease Care**

One hundred sixty-three loci have been linked to IBD, including 30 CD-specific loci and 23 UC-specific loci. However, these genes represent only 23% and 16% of the heritability of CD and UC, respectively, and are thus of limited utility in predicting who will develop IBD.

Genetic testing for IBD and its future clinical use may prove to be of greater benefit in predicting disease course. An example of this potential can be seen in CD with *NOD2*, for which more than 27 variants have been reported (although 3 of these predict most clinical behavior). *NOD2* variants have been associated with fibrostenotic CD, an earlier need for surgery, and the risk of postoperative recurrence of CD. A prior meta-analysis showed a specificity of 98% for complicated CD in those with 2 mutant *NOD2* alleles, leading to the recommendation that more aggressive treatment strategies should be considered for these patients.

Studies have addressed genotype-phenotype associations with other CD susceptibility loci such as *ATG16L1*, *IRGM*, and *IL23R*. These studies have shown more variable results, prompting debate about their utility. Alternatively, the contribution of overall genetic burden of risk alleles (as opposed to associations with individual polymorphisms) in contributing to CD risk has been shown to predict subphenotypes such as ileal involvement. The genetic burden of these risk alleles in CD patients, however, did not show a significant association with complicated disease behavior after adjusting for confounding with ileal location, causing some physicians to question the utility of genetic testing in clinical practice.

Although prior studies of UC have suggested loci conferring increased risk of severe disease, the utility of genetic testing for UC remains unclear following more recent studies that did not show an association between UC disease course and UC-specific loci.

The risk of harmful side effects of IBD therapies may also be identified through genetic testing. A genome-wide association study found a 2.5-fold risk of pancreatitis in IBD patients taking thiopurines who had the single nucleotide polymorphism rs2647087 within the class II human leukocyte antigen region. An association of polymorphisms of *IL23R* has also been reported for psoriasiform reactions to infliximab. As genetic testing becomes more accessible, it may become easier to predict, and therefore easier to avoid, side effects such as these or other rare events, including drug-induced liver injury with anti-TNF agents, for which genetic risk factors have not yet been identified.

Assessing risk in IBD patients by means of genetic testing may also provide clinically meaningful information when combined with additional patient data. For example, a model evaluating *NOD2* genotype and serologies for IBD (ASCA-IgA, ASCA-IgG, anti-OmpC, anti-CBir1, anti-*Pseudomonas fluorescens*-associated sequence I2 [anti-I2], and perinuclear antineutrophil cytoplasmic antibody) has predicted complicated CD with high accuracy. Analysis of a model combining genetic and clinical risk factors showed a significantly increased success rate in predicting the need for surgery as compared to a purely genetic model. This approach may be of particular value, as genetic information for a patient does not exist in a vacuum in clinical practice and would accompany a clinician’s knowledge of the patient’s clinical risk fac-
tors. Combined genetic and microbial analysis has also supported the role of human genetic factors in microbial alterations in specific IBD populations, including a microbial shift characterized by a decrease in *Clostridium* groups XIVa and IV as well as an increase in Actinobacteria and Proteobacteria associated with patients carrying NOD2 risk alleles. Given the multifactorial influences on IBD expression, combining information from these modalities may provide improved accuracy in predicting outcomes for individual patients.

**The Role of the Microbiota in Personalized Inflammatory Bowel Disease Care**

While a complete review of the literature evaluating the microbiota of IBD patients is beyond the scope of this article, it is important to note that advances in microbial analysis have the potential to guide the future care of IBD patients. In fact, the microbiome may be particularly helpful in predicting disease severity in IBD patients. The depletion of *Faecalibacterium prausnitzii*, a butyrate-producing species from the Firmicutes phylum, has been widely reported in CD and has been shown to be decreased in patients with active disease. A relative paucity of *F prausnitzii*, as well as the butyrate-producing species *Roseburia hominis*, has also been shown to correlate with increasing disease severity in UC. Using microbiome sequencing, other researchers have suggested that alterations in the microbiota in the setting of disease flares may be patient-specific. However, the ability to sequence the microbiomes of IBD patients and monitor them for change may ultimately provide a more personalized model for prediction of flares.

Microbial analysis also has the potential to further inform therapeutic decisions in IBD. In fact, corticosteroid responsiveness in IBD has been predicted by the presence of increasing microbial diversity. Similarly, a decrease in bacteria associated with dysbiosis, such as *Escherichia coli*, has been observed in CD patients following treatment with adalimumab. Dysbiosis may also ultimately guide decisions for the continuation of medication, as a low proportion of *F prausnitzii* and a low rate of *Bacteroides* have been shown to predict CD relapse after discontinuation of infliximab.

The role that unique microbial profiles play in IBD may also be seen in fecal microbiota transplantation (FMT). Although studies have shown mixed success with FMT for IBD, closer evaluation of the microbiota of these patients may provide a clue as to the pathogenesis and potential treatment of IBD. Initial findings by Moayyedi and colleagues indicated that FMT did not have a significant effect; however, the inclusion of 22 patients who received FMT from a single donor resulted in a statistically significant benefit, suggesting that donor microbiota characteristics may vastly alter outcomes.

In a second trial, patients deriving benefit from FMT acquired microbial signatures similar to those of their donors, suggesting that the transfer of specific bacterial flora or compounds they produce may be the key to successful FMT in IBD patients. Mouse models showed that the intragastric transfer of *F prausnitzii* cultures or their supernatants significantly decreased colitis severity, further supporting this concept. With further identification of specific microbial profiles that may serve as crucial transferrable elements in FMT, future testing may provide for the proper selection of ideal candidates and donors for the procedure or even potential microbial therapeutics.

**Conclusion**

Current strategies allow clinicians to better target drugs and optimize therapies based upon drug levels and identifiable risk factors for an aggressive disease course. Prospective studies will continue to fill in details of when to test and what levels are needed to achieve the outcome of deep remission with clinical and endoscopic healing. The emerging understanding of genetics and the gut microbiota will also play a role in defining the risks of disease complications, response to therapy, and even risks of therapies. The future of IBD management will include many personalized data points to better predict outcomes for individual patients and to precisely tailor therapy.

**References**


Dr Abreu has been a consultant for AbbVie Laboratories, Prometheus Laboratories, Takeda, UCB, Pfizer, Janssen, and Eli Lilly. She is also an advisory board member for AbbVie Laboratories, and is a scientific advisory board member for Celgene Corporation. Dr Kingsley has no relevant conflicts of interest to disclose.


