TNF Blockers for IBD: Drug and Anti-drug Antibody Levels

Laboratory Support of Management

CLINICAL BACKGROUND

Tumor necrosis factor (TNF) blockers, such as adalimumab (Humira®), infliximab (Remicade®), and the infliximab biosimilar infliximab-dyyb (Inflectra®), are used to treat inflammatory bowel disease (IBD) (Crohn disease, ulcerative colitis) and rheumatic diseases (eg, rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis).[1-3] TNF blockers have had a major impact on the course of treatment for these conditions, but response rates vary by indication (**Table 1**) and other factors (eg, dose, smoker vs non-smoker, etc.). While some patients respond to treatment, many others are refractory to treatment, showing either nonresponse during induction (primary failure) or response during induction followed by loss of efficacy (secondary failure).

When treatment fails, a physician may need to consider other treatment options, such as adjusting dose or dosing intervals, switching to a different TNF blocker, or switching to a non-TNF blocker. Strategies for addressing treatment failure include the following:

- Empiric dose escalation: increasing the dose (eg, from 5 mg to 10 mg) as a first response to failure
- Testing-based strategy: relying on characteristics related to treatment failure to guide therapy; characteristics include pharmacodynamic (PD, presence of drug but lack of efficacy) or pharmacokinetic (PK, lack or absence of detectable drug after treatment) conditions

With a testing-based strategy, measuring TNF blocker drug levels can help differentiate PD from possible PK conditions associated with treatment failure. Drug levels are typically assessed just before administration of the next dose to examine whether trough levels are therapeutic or subtherapeutic.[4] The presence of therapeutic trough levels, particularly in the absence of anti-drug antibodies (ADAs), can indicate PD conditions that are likely related to TNF-independent disease. On the other hand, subtherapeutic trough levels can indicate different types of issues, depending on whether ADAs have formed against the drug.[5,6]

ADAs can cause subtherapeutic trough levels and reduce treatment efficacy by (1) forming ADA-drug complexes that lead to accelerated drug clearance and (2) directly preventing the drug from binding TNF.[7] The reported incidence of ADA formation varies widely, depending on study factors such

Table 1. Incidence of Adalimumab and Infliximab Treatment Failure in IBD

Indication	Adalimumab[1,a]	Infliximab and infliximab-dyyb[2,3,a]
Crohn disease	Week 26: 60%[b] Week 56: 64%[b]	Week 30: 54%-61%[a,b] Week 54: 66%-75%[a,b]
Pediatric Crohn disease	Week 26: 41%-52%[a,c] Week 52: 58%-72%[a,c]	Week 30: 27%-53%[a,d] Week 54: 36%-67%[a,d]
Ulcerative colitis	Week 8: 83%[e] Week 52: 83%[e]	Week 8: 61%-68%[a,e] Week 54: 65%-66%[a,e]
Pediatric ulcerative colitis	Not indicated	Week 8: 67%[f] Week 54: 62%-82%[a,f]

IBD, inflammatory bowel disease; TNF, tumor necrosis factor.
[a]Study design, dosage regimens, and patient population varied by drug and disease. Ranges are presented in this table if multiple doses or trial arms were presented in the package insert. See package insert for specific information.
[b]Treatment failure measured as a lack of clinical remission (clinical remission defined as Crohn disease activity index [CDAI] <150). Analysis included patients with secondary failure after achieving an induction response.
[c]Treatment failure measured as clinical nonresponse (clinical response defined as a decrease of pediatric CDAI [PCDAI] of ≥15 points from baseline). Analysis included patients with primary or secondary failure.
[d]Treatment failure measured as clinical nonresponse (clinical response defined as a decrease of PCDAI of ≥15 points from baseline and total score ≤30). Analysis included patients with primary or secondary failure.
[e]Treatment failure measured as a lack of clinical remission (clinical remission defined as a disease activity score ≤2 and no individual subscores >1). Analysis at week 8 included patients with primary failure. Subsequent analysis included patients with primary or secondary failure.
[f]Treatment failure measured as a lack of clinical remission (clinical remission defined as Pediatric Ulcerative Colitis Activity Index [PUCAI] of <10 points). Analysis at week 8 included patients with primary failure. Subsequent analysis included patients with secondary failure.

as assay methodology and disease state. Reported rates of ADA formation are up to 54% for adalimumab-treated, 83% for infliximab-treated, and 52% for infliximab-dyyb–treated patients.[8]

Patients who have subtherapeutic trough levels of the drug and test negative for ADAs may have nonimmune PK issues, such as increased drug clearance due to nonimmune mechanisms or patient adherence issues.[5,6] Nonimmune PK issues can be managed by administering a higher dose, shortening the dosing interval, or addressing patient adherence.[5,6] However, in patients who have subtherapeutic trough levels and test positive for ADAs, switching to a different TNF blocker may be more effective than increasing dose.[5,6,9] Therefore, testing for ADAs in addition to assessing drug level can help determine which changes in treatment approach are most appropriate.

The American Gastroenterology Association (AGA) suggests a testing-based strategy when control of active IBD is suboptimal.[10] Furthermore, comparisons of empiric and testing-based strategies in infliximab-treated patients with IBD suggest that the testing-based strategy is more cost-effective.[11-13] A testing-based strategy is also associated with beneficial health outcomes such as a higher endoscopic remission rate, higher response rate, and fewer flares requiring clinical care in patients with IBD receiving infliximab.[14]

INDIVIDUALS SUITABLE FOR TESTING

- Individuals with IBD who have recently started treatment with adalimumab, infliximab, or the biosimilar infliximab-dyyb (baseline testing)
- Individuals who experience treatment failure with any of these drugs

TEST AVAILABILITY AND SELECTION

Quest Diagnostics offers tests for the TNF blockers adalimumab and infliximab (including infliximab-dyyb) for patients with IBD (**Table 2**). All tests use enzyme-linked immunosorbent assays (ELISA) to measure levels.

Testing for drug levels will indicate bioavailability, whereas testing for ADAs can help differentiate causes of insufficient bioavailability.

- Measuring only drug levels may be appropriate if a sequential approach is preferred to concurrent testing. It may also be appropriate for therapeutic drug monitoring (TDM), though TDM is not routine for TNF blocker treatment because thresholds and testing intervals have not been established.
- Measuring only ADAs may be appropriate if insufficient bioavailability has already been established.
- Measuring both drug and ADA levels at the same time may expedite identification of the bioavailability of the drug and the cause of treatment failure.

Table 2. Available Tests for TNF Blockers for IBD

Test code	CPT code(s)*	Test name	Clinical use
36298[a]	80145	Adalimumab Level for IBD	Determine adalimumab levels
36294[a]	83520	Adalimumab Anti-drug Antibody for IBD	Determine presence of antibodies to adalimumab
36296[a]	83520, 80145	Adalimumab Level and Anti-drug Antibody for IBD	Determine adalimumab levels and presence of antibodies to adalimumab
36303[a,b]	80230	Infliximab Level for IBD	Determine infliximab and infliximab-dyyb (Inflectra®) levels
36301[a,b]	83520	Infliximab Anti-drug Antibody for IBD	Determine presence of antibodies to infliximab and infliximab-dyyb (Inflectra®)
36311[a,b]	83520, 80230	Infliximab Level and Anti-drug Antibody for IBD	Determine infliximab and infliximab-dyyb (Inflectra®) levels and presence of antibodies to infliximab and infliximab-dyyb (Inflectra®)

IBD, inflammatory bowel disease; TNF, tumor necrosis factor.

[a]This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics. It has not been cleared or approved by the US Food and Drug Administration. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

[b]Infliximab assays are validated for the infliximab biosimilar infliximab-dyyb (Inflectra®) with no analytical differences between these drugs.

TEST INTERPRETATION

The AGA suggests an optimal adalimumab trough concentration of ≥7.5 µg/mL and an optimal infliximab trough concentration of ≥5 µg/mL in patients with active IBD on maintenance therapy.[10] However, data from separate clinical studies suggest an optimal adalimumab trough concentration of >4.5 µg/mL or 8 to 12 µg/mL, and an optimal infliximab trough concentration of >3.8 µg/mL or 6 to 10 µg/mL.[15,16] Subtherapeutic drug levels may be caused by inadequate dosing, a dosing interval that is too long, accelerated drug clearance, or a patient not yet achieving a steady state trough level early in therapy.

Adalimumab or infliximab ADA levels ≥10 AU indicate detectable serum levels, which can lead to accelerated drug clearance, reduced trough levels, and a compromised clinical response. Levels <10 AU are considered "not detected" and suggest that treatment failure is not caused by ADAs. Quest assays test for total ADA (ie, measure free and bound ADA). Some ELISA-based tests for adalimumab or infliximab ADAs are susceptible to inaccurate results caused by cross-reactivity with RF. However, Quest has developed ADA ELISAs that are not impacted by the presence or absence of RF.

Test interpretation for infliximab assays applies to both infliximab and infliximab-dyyb.

Table 3 contains result interpretation and management strategies when both drug and ADA levels are tested.

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Table 3. Interpretation of Results in Patients with TNF Blocker Treatment Failure[11,17]

	ADA not detected (absent)	ADA detected (present)
Drug levels subtherapeutic	• Suggests insufficient bioavailability caused by nonimmune PK or patient adherence issues • Consider increasing therapeutic dose or addressing potential adherence issues	• Suggests insufficient bioavailability caused by immunogenicity • Consider switching to different TNF blocker
Drug levels therapeutic	• Suggests PD issue caused by TNF-independent disease • Consider switching to a non-TNF treatment	• Rare situation that may be caused by a false-positive result or nonfunctional ADAs • Consider retest or testing for neutralizing antibody by cell-based assay

ADA, anti-drug antibody; PD, pharmacodynamic; PK, pharmacokinetic; TNF, tumor necrosis factor.

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