TNF Blockers for Rheumatic Diseases: 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 rheumatic diseases (eg, rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis) and inflammatory bowel disease (IBD) (Crohn disease, ulcerative colitis).[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 interval, 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) 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 as assay methodology and disease state. Reported rates of ADA

Table 1. Incidence of Nonresponse to Adalimumab and Infliximab for Treatment of Rheumatic Diseases

Indication	Adalimumab[1,a,b]	Infliximab and infliximab-dyyb[2,3,a]
Ankylosing spondylitis[c]	Week 12: 42% Week 24: ~50%	Week 12: ~40% Week 24: 40%
Plaque psoriasis[d]	Week 16: 29% Week 52: 21%	Week 10: 25%-30%[a] Week 50: ~45%-70%[a]
Psoriatic arthritis[e]	Week 12: 42% Week 24: 43%	Week 14: 42% 6 months: 46%
Rheumatoid arthritis[e]	Week 52: 27% (MTX-naïve)[f] Week 104: 31% (MTX-naïve)[f]	Week 30: 42%-50% (MTX-nonresponse)[a,f] Week 54: 41%-58% (MTX-nonresponse)[a,f] Week 54: 34%-38% (MTX-naïve)[a,f]

ACR, American College of Rheumatology; ASAS, Assessment in SpondyloArthritis International Society; MTX, methotrexate; PASI, Psoriasis Area and Severity Index.

[a]Study design, dosage regimens, and patient population (eg, methotrexate-naïve vs no response to methotrexate) 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]Adalimumab is also indicated for treatment of juvenile idiopathic arthritis, hidradenitis suppurativa, and uveitis. See package insert for response rates.[1]

[c]Nonresponse is defined as not meeting ASAS 20 response (≥20% improvement for ASAS response criteria; for adalimumab, a 10-unit improvement on the Visual Analog Scale was also factored in).

[d]Nonresponse is defined as not meeting PASI 75 response (PASI score improvement of ≥75% from baseline).

[e]Nonresponse is defined as not meeting ACR 20 response (≥20% improvement for ACR response criteria).

[f]In combination with methotrexate.

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] 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.[5,7] Therefore, testing for ADAs in addition to assessing drug level can help determine which changes in treatment approach are most appropriate.

INDIVIDUALS SUITABLE FOR TESTING

- Individuals with a rheumatic disease who have experienced failure of treatment with adalimumab, infliximab, or the infliximab biosimilar infliximab-dyyb

TEST AVAILABILITY AND SELECTION

Quest Diagnostics offers tests for the TNF blockers adalimumab and infliximab (including infliximab-dyyb) for patients with rheumatic diseases (**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.

TEST INTERPRETATION

Studies suggest a target trough concentration of 5 to 12 µg/mL for adalimumab[9] and 2 to 8 µg/mL or 2 to 10 µg/mL for infliximab.[10,11] Subtherapeutic drug levels may be caused by a patient not yet achieving a steady state trough level early in therapy; they may also be caused by inadequate dosing, a dosing interval that is too long, or accelerated drug clearance.

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.

Table 2. Available Tests for TNF Blockers for Rheumatic Diseases

Test code	CPT code(s)*	Test name	Clinical use
36299[a]	80145	Adalimumab Level for Rheumatic Diseases	Determine adalimumab levels
36295[a]	83520	Adalimumab Anti-drug Antibody for Rheumatic Diseases	Determine presence of antibodies to adalimumab
36297[a]	83520, 80145	Adalimumab Level and Anti-drug Antibody for Rheumatic Diseases	Determine adalimumab levels and presence of antibodies to adalimumab
36310[a,b]	80230	Infliximab Level for Rheumatic Diseases	Determine infliximab and infliximab-dyyb (Inflectra®) levels
36302[a,b]	83520	Infliximab Anti-drug Antibody for Rheumatic Diseases	Determine presence of antibodies to infliximab and infliximab-dyyb (Inflectra®)
36312[a,b]	83520, 80230	Infliximab Level and Anti-drug Antibody for Rheumatic Diseases	Determine infliximab and infliximab-dyyb (Inflectra®) levels and presence of antibodies to infliximab and infliximab-dyyb (Inflectra®)

[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.

Table 3. Interpretation of Results in Patients with TNF Blocker Treatment Failure[6]

	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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* The CPT codes provided are based on AMA guidelines and are for informational purposes only. CPT coding is the sole responsibility of the billing party. Please direct any questions regarding coding to the payer being billed.