

Optimizing Biologic Therapy in Rheumatic Disease



DoseASSURE™, Labcorp’s portfolio of biologics monitoring assays, may help physicians optimize biological therapy using a personalized, patient-specific approach by:

- Aiding in titrating doses and adjusting frequency to maximize effectiveness^{1,2}
- Identifying lack of response due to non-compliance or under-treatment³
- Assisting in preventing and managing loss of response due to immunogenicity^{1,4}
- Predicting which patients are likely to retain long-term response⁵
- Minimizing cost to patient by avoiding unhelpful dose escalation⁶
- Avoiding overtreatment in low disease activity cases where tapering down is desirable⁷
- Elucidating poor response as due to undertreatment (pharmacokinetic), mechanistic mismatch (pharmacodynamic) or development of anti-drug antibodies (immunogenic)

Biologic Drug Name	Primary Target*	Clinical Indications*	Test Name	Test No.
Adalimumab (Humira®)	TNF	CD, UC, RA	Adalimumab and Anti-Adalimumab Antibody, <i>DoseASSURE™</i> ADL	503890
Certolizumab (Cimzia®)	TNF	CD, RA, PA, PP	Certolizumab and Anti-Certolizumab Antibody, <i>DoseASSURE™</i> CTZ	504627
Etanercept (Enbrel®)	TNF	RA, JIA, PA, PP, AS	Etanercept and Anti-Etanercept Antibody, <i>DoseASSURE™</i> ETN	504245
Golimumab (Simponi®)	TNF	UC, RA	Golimumab and Anti-Golimumab Antibody, <i>DoseASSURE™</i> GOL	504563
Infliximab (Remicade®; Avsola™, Renflexis®)	TNF	CD, UC **	Infliximab and Anti-Infliximab Antibody, <i>DoseASSURE™</i> IFX	503870
Rituximab (Rituxan®)	CD20	RA, NHL, CLL	Rituximab and Anti-Rituximab Antibody, <i>DoseASSURE™</i> RTX	504355
Ustekinumab (Stelara®)	IL23, IL12	CD, PA, PP	Ustekinumab and Anti-Ustekinumab Antibody, <i>DoseASSURE™</i> UST	504594

* Partial listing of FDA-approved indications. TNF: tumor necrosis factor, IL: interleukin, CD: Crohn’s Disease, UC: Ulcerative Colitis, RA: Rheumatoid Arthritis, PA: Psoriatic Arthritis, PP: Plaque Psoriasis, JIA: Juvenile Idiopathic Arthritis, AS: Ankylosing Spondylitis, NHL: Non-Hodgkin’s Lymphoma, CLL: Chronic Lymphocytic Leukemia
 ** Published validation study, Marini JC, et al. Comparisons of Serum Infliximab and Antibodies-to-Infliximab Tests Used in Inflammatory Bowel Disease Clinical Trials of Remicade® AAPS Journal 2016. DOI: 10.1208/s12248-016-9981-3

DoseASSURE test portfolio provides tests for both drug concentration (TDM) & anti-drug antibody (immunogenicity)

Therapeutic Drug Monitoring (TDM)

- Biologics have variable pharmacokinetics.^{2,4}
- Dosing by weight and empiric dose adjustment may be inefficient and suboptimal.^{2,6}
- Clinical efficacy in RA and/or psoriasis has been shown to correspond with serum concentrations of infliximab, adalimumab, etanercept, golimumab, rituximab, and ustekinumab.^{4,8-14}
- TDM for biologics is a valuable tool to evaluate doses and to tailor dose adjustments to your individual patient.^{1-4,6}
- TDM can help differentiate non-compliance and under-treatment from other causes of lack of response.³
- Personalized treatment using TDM has been shown to improve both clinical and cost-effectiveness in RA.⁶

Immunogenicity Testing (Anti-drug Antibody level)

- All biologics have the potential to induce an antibody-mediated immune response.^{1,15}
- As many as one third of RA patients on biological therapy may develop anti-drug antibodies.^{15,16}
- Anti-drug antibodies may appear as early as 2 weeks or as late as 3 years after the first infusion.¹⁷
- Co-therapy with methotrexate, sufficient drug levels, and maintenance dosing (vs. episodic or on-demand use) reduce the risk of anti-drug antibody formation.¹⁵⁻²⁰
- Anti-drug antibodies can adversely affect the amount of drug in the body.^{1,15,16,19} Therefore, concomitant measurement of anti-drug antibodies is an important adjunct to TDM for biologics.

Interpreting Drug Concentrations

- Higher drug trough levels have been correlated with clinical improvement as well as to higher rates of response and remission in rheumatic diseases.^{4,8-13}
- A consensus has yet to be reached about target ranges and maximally effective concentrations.¹

Optimal drug concentration depends on the disease and the desired therapeutic endpoint.

Interpreting Anti-Drug Antibody Levels

- Anti-drug antibodies may impact pharmacokinetics, efficacy, and cost-effectiveness.
- Low titer antibodies may have little or no effect on drug levels or clinical outcome. In fact, they may be transient and disappear over time, or they may progress to increasing titers.^{1,16,18,21}
- In contrast, high titers of antibodies are likely to be more consequential, leading to loss of drug efficacy by preventing drug binding to TNF and/or increasing drug clearance.^{1,16,19}

Anti-drug antibody positivity should be interpreted in the context of the concomitant free drug level.

Drug	Normal half-life	Proposed Target Trough Concentrations§	Other clinical data on Trough Concentrations
Adalimumab	Approx. 2 weeks	5 - 8 µg/mL in RA9; 5 - 8 µg/mL in PA22; 3.5 - 7.0 µg/mL in psoriasis ²³	
Certolizumab	Approx. 2 weeks	>23 µg/mL corresponded to better EULAR response rates. ²⁴	A definitive target range has yet to be determined.
Etanercept	3 - 5.5 days	> 3.1 µg/mL (at 3 months predicted response at 6 months in RA) ²⁵	In RA, good responders had higher levels (median 3.8 µg/mL 2.5 - 5.2) compared to non-responders (2.8 µg/mL 1.3 - 3.9). ¹⁰ In AS, clinical responders (ASDAS) had higher median levels (median 3.8 µg/mL, 2.5 - 5.2) than non-responders (2.3 µg/mL, 1.2 - 3.4). ⁵
Golimumab	Approx. 2 weeks	No consensus on clinical recommendation for RA	In RA, higher levels (median 3.4 µg/mL) were associated with a greater rate of clinical response (ACR20). ¹¹
Infliximab	7.7 to 9.5 days	< 2 µg/mL: low and ≥ 8 µg/mL: high in RA2	In RA, responders had higher levels (median 3.6 µg/mL, 1.4 - 8.2) than non-responders (0.5 µg/mL, 0.2 - 2.2). ⁸
Rituximab	18 days (5.2-77.5 days)	No consensus on clinical recommendation for RA	
Ustekinumab	Approx. 3 weeks	A definitive target range has yet to be determined	In psoriasis, PASI 50 responders had higher trough concentrations than non-responders. ¹⁴

§Note: These target ranges were those used in landmark studies and do not necessarily translate into general recommendations for individual patients.

When & where to collect blood on my patients?

- The timing of sample collection is important because the drug concentration will change during the dosing interval.
- The Trough Concentration (TC) is measured at the least variable time in the dosing interval, just before the next dose (same day to within <7 days depending on the drug's normal half-life).
- During induction and maintenance phases, trough collections are usually recommended because target ranges are defined using TC.
- Blood can be drawn at any of Labcorp's nearly 2000 patient service centers located nationwide.

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