MAYO CLINIC LABORATORIES

Test Definition: ADALX

Adalimumab Quantitative with Reflex to Antibody, Serum

Overview

Useful For

Therapeutic drug monitoring of adalimumab

Evaluating patients for loss of response, partial response on initiation of therapy, autoimmune or hypersensitivity reactions, primary nonresponse, reintroduction after drug holiday, endoscopic/computed tomography enterography recurrence (in inflammatory bowel disease), acute infusion reactions and proactive monitoring including reflex testing for antibodies to adalimumab

This test **does not** differentiate between the originator and biosimilar products.

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
ADLAB	Adalimumab Ab, S	No	No

Testing Algorithm

If the result is 8.0 mcg/mL or less, then adalimumab antibody test will be performed at an additional charge.

For more information see Ulcerative Colitis and Crohn Disease Therapeutic Drug Monitoring Algorithm.

Special Instructions

- Ulcerative Colitis and Crohn Disease Therapeutic Drug Monitoring Algorithm

Highlights

Adalimumab is a fully human therapeutic monoclonal antibody targeting tumor necrosis factor-alpha, a proinflammatory cytokine that is upregulated in several autoimmune inflammatory states.

Testing for adalimumab concentration and the presence of anti-adalimumab antibodies is useful to adjust therapeutic strategies for patients starting therapy (proactive monitoring) and dosing or treatment strategy when partial response or loss of response to therapy is observed, manifested as recurrence of symptoms.

Method Name

Enzyme-Linked Immunosorbent Assay (ELISA)

NY State Available

Yes

Specimen

Specimen Type
Serum

Ordering Guidance
If both quantitation and antibody testing are needed, regardless of the quantitation results, order ADALP / Adalimumab Quantitative with Antibody, Serum

Specimen Required
Patient Preparation: For 12 hours before specimen collection, patient **should not** take multivitamins or dietary supplements (eg, hair, skin, and nail supplements) containing biotin (vitamin B7)
Supplies: Sarstedt Aliquot Tube, 5 mL (T914)
Collection Container/Tube:
Preferred: Serum gel
Acceptable: Red top
Submission Container/Tube: Plastic vial
Specimen Volume: 0.5 mL Serum
Collection Instructions:
1. Draw blood immediately before the next dose of drug administration (trough specimen).
2. Centrifuge and aliquot serum into a plastic vial.

Forms
If not ordering electronically, complete, print, and send one of the following with the specimen:
-Gastroenterology and Hepatology Test Request (T728)
-Therapeutics Test Request (T831)

Specimen Minimum Volume
Serum: 0.35 mL

Reject Due To

Gross hemolysis	OK
Gross lipemia	OK
Gross icterus	OK
Heat-treated specimen	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container

Serum	Refrigerated (preferred)	28 days	
	Frozen	28 days	

Clinical & Interpretive

Clinical Information

Drug and target:
Adalimumab (ADL) is a monoclonal antibody (IgG1 kappa) which targets tumor necrosis factor (TNF)-alpha. TNF-alpha binds to TNF-alpha receptors, leading to the inflammatory response of autoimmune diseases. By binding to TNF-alpha, ADL can reduce the inflammatory response. Because TNF-alpha is also a part of the immune system that protects the body from infection, treatment with ADL may increase the risk of infections. Biosimilars have the same primary amino acid sequence as the reference or originator product. Therefore, ADL will be used to refer to both the reference product and the biosimilar products interchangeably. This test cannot distinguish between the reference product Humira and the ADL biosimilars products.

Indications:
Adalimumab is a subcutaneously administered. It is US Food and Drug Administration-approved for the treatment of multiple immune-mediated inflammatory diseases, including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis, Crohn's disease (adults and pediatric patients > or =6 years), ulcerative colitis (adults), hidradenitis suppurativa, juvenile idiopathic arthritis (> or =2 years), and non-infectious uveitis. Standard adult maintenance dosing is typically 40 mg subcutaneously every other week, with disease-specific induction regimens for inflammatory bowel disease and hidradenitis suppurativa. Dose escalation to weekly administration may be used in selected patients with inadequate clinical response.

Pharmacokinetics highlights:
Adalimumab has a half-life of approximately 2 weeks. It is usually given as a fixed dose (not weight-based). Peak serum concentrations are achieved approximately 5 days post-dose. Steady-state concentrations are achieved by 3 to 5 months of repeated dosing. Clearance of ADL can be influenced by similar factors as other anti-TNFs: high inflammatory burden, low albumin, and large body mass can increase clearance, while concurrent immunomodulators can reduce immunogenicity and clearance. There is considerable inter-patient variability.

Immunogenicity:
Around 30% of patients have no primary response to anti-TNF therapy, and up to 60% of initial responders experience secondary loss of response over time and require either drug dose-escalation or a switch to an alternative therapy in order to maintain response.(1) Reasons for primary loss of response may include disease processes mediated by proinflammatory molecules other than TNF. Secondary loss of response is associated with low serum albumin, high body-mass index, the degree of systemic inflammation and development of immunogenicity.(2,3) Antidrug antibody formation may increase drug clearance in treated patients or neutralize the drug effect, thereby potentially contributing to the loss of response. Antidrug antibodies (ADA) could also cause adverse events such as serum sickness and hypersensitivity reactions.(4) In clinical studies, the incidence of ADA formation varied with dose, concomitant immunosuppressants, and indication, and the presence of antibodies-to-adalimumab (ATA) was associated with lower serum ADL concentrations and, in some analyses, reduced clinical response. Concomitant methotrexate has been shown to reduce the frequency of ATA formation compared with ADL monotherapy. Measurement of ATA is dependent on

assay sensitivity and drug tolerance, and comparisons should be made with caution. The clinical implications of ATA positivity should be interpreted in the context of drug concentrations, clinical response, and immunogenicity assay characteristics.

Evidence for therapeutic drug monitoring:
Adalimumab therapeutic drug monitoring (TDM) is supported by evidence for both reactive and proactive strategies. Reactive TDM is performed in the setting of loss of response or infusion reactions.(5) Reactive TDM is well validated to distinguish pharmacokinetic failure (low drug, absent antibodies) from immunogenicity (anti-drug antibodies), enabling rational dose escalation or switching and improving cost-effectiveness. Proactive TDM studies, involving routine measurement during maintenance stages of therapy, suggests benefits in reducing immunogenicity, maintaining remission, and optimizing long-term exposure, particularly early in therapy and in high-risk patients.(6,7)

Reference Values

ADALIMUMAB QUANTITATIVE:
Limit of quantitation is 0.8 mcg/mL. Optimal therapeutic ranges are disease specific.

ADALIMUMAB ANTIBODY:
<14.0 AU/mL

Interpretation

Low trough concentrations may be associated with loss of response to adalimumab (ADL) due to possible development of an immune response to ADL. Testing for antibodies-to-adalimumab (ATA) is suggested in patients with trough concentrations less than 8.0 mcg/mL.

Adalimumab trough concentrations greater than or equal to 8.0 mcg/mL in patients with loss of response to therapy may suggest possible benefit of treatment with a different monoclonal antibody therapy.

Adalimumab concentrations greater than or equal to 35 mcg/mL suggest possible testing at a time point other than trough and should be evaluated within the clinical context of the patient.

Interpretation and patient management will be different according to disease state, clinical presentation (symptomatic versus appropriate response to therapy), several other laboratory tests and a combination of the drug concentration and/or presence of anti-drug-antibodies.

In the setting of loss of response to ADL therapy for adults with active inflammatory bowel disease (IBD), a clinical decision tool from the American Gastroenterology Association (5,8) suggests the following scenarios for a blood draw that occurred at trough, immediately before the next injection dose:
-For patients who have undetectable or low concentrations of ADL (<8 mcg/mL) but no detectable ATA, the patient care team may choose to increase the dose of ADL in an attempt to increase the amount of the drug in circulation.
-If the patient has subtherapeutic ADL concentrations (<8 mcg/mL) in the presence of an ATA, the patient care team may switch the patient to another tumor necrosis factor inhibitor.
-For patients with increased trough concentrations of ADL (therapeutic or greater), whether an ATA is present or not, it may be necessary to switch the patient to a therapy with a different mechanism of action such as the anti-alpha4-beta-7-integrin antibody vedolizumab or the interleukin (IL)-12/IL-23 antibodies.

Test interpretation relies on clinical presentation and may differ from the statements above, which were designed for adults with IBD experiencing loss of response. For individuals on ADL therapy for other conditions such as rheumatoid arthritis, or pediatric patient populations or proactive monitoring, drug concentration therapeutic targets and patient management decision may be individualized. When both the drug quantitation and anti-drug-antibodies are ordered, an interpretive guide is offered below.

Adalimumab quantitation, mcg/mL	**Antibody-to-adalimumab, AU/mL**	**Comment**
<8.1	Negative (<14.0)	Absence of detectable antibody-to-adalimumab (ATA). Low concentration of adalimumab (ADL) may be attributable to other parameters related to ADL clearance.
<8.1	Positive (> or =14.0)	Presence of ATA detected, which correlates with low concentration of adalimumab (ADL). ATA may be associated with increased clearance and lower circulating concentrations of ADL.
8.1-15.0	Negative (<14.0)	Absence of detectable antibody-to-adalimumab (ATA). At this concentration of adalimumab (ADL), a low-titer (14.0-149.9 AU/mL) or moderate titer (150.0-500.0 AU/mL) ATA cannot be excluded. However, the presence of a high-titer ATA (> or =500.0 U/mL) is unlikely. If there is clinical suspicion for a low-titer ATA, suggest submission of a new sample obtained at trough. This test has demonstrated ADL tolerance up to 40.0 mcg/mL for ATA > or =500.0 AU/mL, up to 15.0 mcg/mL for ATA between 150.0-500.0 and up to 8.0 mcg/mL for ATA between 14.0-149.9 AU/mL.
8.1-15.0	Low or moderate positive (14.0-499.9)	Presence of antibody-to-adalimumab (ATA) detected. At this concentration of adalimumab (ADL), the detected titer of the ATA may be modestly underestimated. This test has demonstrated ADL tolerance up to 40.0 mcg/mL for ATA > or =500.0 AU/mL, up to 15.0 mcg/mL for ATA between 150.0-500.0 and up to 8.0 mcg/mL for ATA between 14.0-149.9 AU/mL.
8.1-15.0	High positive (> or =500.0)	Presence of antibody-to-adalimumab (ATA) detected. This test has demonstrated adalimumab tolerance up to 40.0

		mcg/mL for ATA > or =500.0 AU/mL, up to 15.0 mcg/mL for ATA between 150.0-500.0 and up to 8.0 mcg/mL for ATA between 14.9-149.9 AU/mL.
>15.0	Negative (<14.0)	At this concentration of antibody-to-adalimumab (ADL), a low (14.0-149.9 AU/mL) or moderate titer (150.0-500.0 AU/mL) antibody-to-adalimumab (ATA) cannot be excluded. The presence of a high-titer ATA (> or =500.0 U/mL) is unlikely but also cannot be completely excluded. If there is clinical suspicion for an ATA, suggest submission of a new sample obtained at trough, preferably during the maintenance phase of therapy. This test has demonstrated ADL tolerance up to 40.0 mcg/mL for ATA > or =500.0 AU/mL, up to 15.0 mcg/mL for ATA between 150.0-500.0 and up to 8.0 mcg/mL for ATA between 14.9-149.9 AU/mL.
>15.0	Low positive (14.0-149.9)	Presence of antibody-to-adalimumab (ATA) detected. At this concentration of adalimumab (ADL), the detected titer of the ATA is likely underestimated. Suggest submission of a new sample obtained at trough, preferably during the maintenance phase of therapy. This test has demonstrated ADL tolerance up to 40.0 mcg/mL for ATA > or =500.0 AU/mL, up to 15.0 mcg/mL for ATA between 150.0-500.0 and up to 8.0 mcg/mL for ATA between 14.0-149.9 AU/mL.
>15.0	Moderate positive (150.0-499.9)	Presence of antibody-to-adalimumab (ATA) detected. At this concentration of adalimumab (ADL), the detected titer of the ATA may be underestimated. Suggest submission of a new sample obtained at trough, preferably during the maintenance phase of therapy. This test has demonstrated ADL tolerance up to 40.0 mcg/mL for ATA > or =500.0 AU/mL, up to 15.0 mcg/mL for ATA between 150.0-500.0 and up to 8.0 mcg/mL for ATA between 14.0-149.9 AU/mL.
>15.0	High positive (> or =500.0)	Presence of antibody-to-adalimumab (ATA) detected. This test has demonstrated adalimumab tolerance up to 40.0 mcg/mL for ATA > or =500.0 AU/mL, up to 15.0 mcg/mL for ATA

		between 150.0-500.0 and up to 8.0 mcg/mL for ATA between 14.0-149.9 AU/mL.

Cautions

Tumor necrosis factor (TNF) measurement is not the analyte of choice for monitoring therapy with TNF inhibitors (such as adalimumab [ADL] or infliximab), since TNF testing would not distinguish between free TNF and TNF bound to the monoclonal antibody, either in the extracellular or membrane-bound form of the cytokine.

While the immunogenicity rates between reference product and biosimilars are similar, there could be epitope differences in the anti-drug-antibodies for each formulation.

Toxicity effects other than acute hypersensitivity infusion reactions have not been described nor correlated with high ADL concentrations.

For patients taking biotin supplements, it is recommended to wait at least 12 hours after the last ingestion of biotin to collect a blood sample for this test.

The presence of ADL in patients' serum is a recognized interference in most adalimumab antibodies (ATA) methods. The ATA assay includes an acid dissociation step, which partially mitigates this interference. The best timeframe for a blood draw for therapeutic drug monitoring is at trough, immediately before the next dose of the medication.

This test is designed to quantify adalimumab regardless of formulation. It is suitable for testing both the reference product and all US Food and Drug Administration and European Medicines Agency-approved biosimilars. The test does not differentiate between the originator and biosimilar products.

Clinical Reference

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Performance

Method Description
Testing for adalimumab and antibodies-to-adalimumab is performed using laboratory-developed immunoassays.(Unpublished Mayo method)

PDF Report
No

Day(s) Performed
Monday, Wednesday, Thursday

Report Available
2 to 4 days

Specimen Retention Time
14 days

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Superior Drive

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Definition: ADALX

Adalimumab Quantitative with Reflex to Antibody, Serum

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

80145
83520 (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
ADALX	Adalimumab QN with Reflex to Ab, S	86894-3

Result ID	Test Result Name	Result LOINC® Value
ADALX	Adalimumab QN with Reflex to Ab, S	86894-3