

Corporate Medical Policy

Measurement of Serum Antibodies to Infliximab, Adalimumab, Vedolizumab and Ustekinumab

File Name:	measurement_of_serum_antibodies_to_infliximab_and_adalimumab
Origination:	9/2012
Last CAP Review:	2/2019
Next CAP Review:	2/2020
Last Review:	2/2019

Description of Procedure or Service

Infliximab (Remicade[®] Janssen Biotech) is an intravenous tumor necrosis factor (TNF) alpha blocking agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and ulcerative colitis.

Adalimumab (Humira[®] AbbVie) is a subcutaneous TNF alpha inhibitor that is FDA-approved for treatment of Crohn's disease and ulcerative colitis in adults only, plus juvenile idiopathic arthritis.

Vedolizumab (Entyvio[®]) is an intravenous integrin receptor antagonist approved by the FDA for the treatment of ulcerative colitis and Crohn's disease. Vedolizumab is generally given for those patients who have had an inadequate response with, lost response to, or were intolerant to TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids. This drug is used for achieving clinical response or remission, or achieving corticosteroid-free remission.

Ustekinumab (Stelara[®]) is an intravenous and subcutaneous human interleukin (IL)-12 and IL-23 antagonist approved by the FDA for the treatment of adult patients with moderately to severely active Crohn's disease, as well as for the treatment of plaque psoriasis and psoriatic arthritis. Ustekinumab is generally administered to patients who have failed or were intolerant to treatment with immunomodulators or corticosteroids, or to treatment with one or more TNF blockers.

Infliximab in autoimmune disease

Infliximab is a chimeric (mouse/human) anti-tumor necrosis factor (TNF) -alpha monoclonal antibody. Adalimumab is a fully human monoclonal antibody to TNF-alpha. Therapy with monoclonal antibodies has revolutionized therapy in patients with inflammatory diseases such as inflammatory bowel disease (Crohn's disease [CD] and ulcerative colitis [UC]), rheumatoid arthritis and psoriasis. These agents are generally given to patients who fail conventional medical therapy, and they are typically highly effective for induction and maintenance of clinical remission. However, not all patients respond, and a high proportion of patients lose response over time. An estimated one-third of patients do not respond to induction therapy (primary nonresponse), and among initial responders, response wanes over time in approximately 20% to 60% of patients (secondary nonresponse). The reasons for therapeutic failures remains a matter of debate but include accelerate drug clearance (pharmacokinetics) and neutralizing agent activity (pharmacodynamics) due to ADA (antidrug antibodies). ADA are also associated with acute infusion reactions (infliximab), injection site reactions (adalimumab) and with delayed hypersensitivity reactions (infliximab). As a fully human antibody, adalimumab is considered less immunogenic than chimeric antibodies, such as infliximab.

Detection of antidrug antibodies

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The detection and quantitative measurement of antidrug antibodies is difficult owing to drug interference and identifying when antibodies have a neutralizing effect. First-generation assays, (i.e., enzyme-linked immunoabsorbant assays [ELISA]) can only measure antidrug antibodies in the absence of detectable drug levels due to interference of the drug with the assay, limiting clinical utility. Other techniques available for measuring antibodies include the radioimmunoassay (RIA) method, and more recently, the homogenous mobility shift assay (HMSA) using high-performance liquid chromatography.

Disadvantages of the RIA method are associated with the complexity of the test and prolonged incubation time, and safety concerns related to the handling of radioactive material. The HMSA has the advantage of being able to measure antidrug antibodies when infliximab is present in the serum. Studies evaluating the validation of the results between different assays are lacking, making interstudy comparisons difficult. One retrospective study in 63 patients demonstrated comparable diagnostic accuracy between 2 different ELISA methods, i.e., double antigen ELISA and antihuman lambda chain ELISA. This study did not include an objective, clinical and endoscopic scoring system for validation of results.

Treatment options for patients with secondary loss of response to anti-TNF therapy

A diminished or suboptimal response to infliximab, adalimumab, vedolizumab or ustekinumab can be managed in several ways: shortening the interval between doses, increasing the dose, switching to a different anti-TNF agent (in patients who continue to have loss of response after receiving the increased dose), or switching to a non-anti-TNF agent. Incorporating therapeutic drug monitoring into clinical practice has been proposed to allow clinicians to optimize treatment by maintaining effective drug concentrations over time and affecting a patient's loss of response. However, currently there are no society guidelines that recommend testing serum levels or levels of antibodies regarding the use of TNF-inhibitor therapy (e.g. infliximab, adalimumab, vedolizumab or ustekinumab).

The measurement of antibodies to include the measurement of serum drug concentrations to adalimumab, infliximab, vedolizumab or ustekinumab include but are not limited to the following tests:

- Prometheus Anser™ ADA
- Prometheus Anser™ IFX
- Prometheus Anser™ VDZ
- Prometheus Anser™ UST

Regulatory Status

Prometheus® Laboratories Inc. offers non-radiolabeled, fluid-phase HMSA tests called Anser™ IFX for infliximab, Anser™ ADA for adalimumab, Anser™ VDZ for vedolizumab and Anser™ UST for ustekinumab. None of these tests are ELISA-based and each can measure antidrug antibodies in the presence of detectable drug levels, improving upon a major limitation of the ELISA method. These tests measure serum drug concentrations and antidrug antibodies.

These tests were developed and their performance characteristics determined by Prometheus Laboratories Inc. None have been cleared or approved by the U.S. Food and Drug Administration. Prometheus Laboratories Inc. is a CAP-accredited Clinical Laboratory Improvement Amendment (CLIA) laboratory.

Related Policies:

Infliximab, Infliximab-dyyb, Infliximab-abda
Vedolizumab (Entyvio)
Ustekinumab (Stelara®)

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*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

Measurement of serum antibodies to infliximab is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Measurement of serum antibodies to adalimumab is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Measurement of serum antibodies to vedolizumab is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Measurement of serum antibodies to ustekinumab is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When measurement of serum antibodies to Infliximab, Adalimumab and Vedolizumab is covered

Not applicable.

When measurement of serum antibodies to Infliximab, Adalimumab and Vedolizumab is not covered

Measurement of antibodies to infliximab in a patient receiving treatment with infliximab, either alone or as a combination test which includes the measurement of serum infliximab levels, is considered investigational.

Measurement of antibodies to adalimumab in a patient receiving treatment with adalimumab, either alone or as a combination test which includes the measurement of serum adalimumab levels, is considered investigational.

Measurement of antibodies to vedolizumab in a patient receiving treatment with vedolizumab, either alone or as a combination test which includes the measurement of serum vedolizumab levels, is considered investigational.

Measurement of antibodies to ustekinumab in a patient receiving treatment with ustekinumab, either alone or as a combination test which includes the measurement of serum ustekinumab levels, is considered investigational.

Policy Guidelines

For individuals who have rheumatoid arthritis, psoriatic arthritis, or juvenile idiopathic arthritis; inflammatory bowel disease (Crohn disease, ulcerative colitis); ankylosing spondylitis; or plaque psoriasis who receive evaluation for anti-tumor necrosis factor α inhibitor antibodies to infliximab or adalimumab, the evidence includes multiple systematic reviews, 1 randomized

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controlled trial (RCT), and observational studies. Relevant outcomes are test accuracy and validity, change in disease status, health status measures, quality of life, and treatment-related morbidity. Antibodies to infliximab (ATI) or to adalimumab (ATA) develop in a substantial proportion of treated patients and are believed to neutralize or enhance clearance of the drugs. Considerable evidence has demonstrated an association between antidrug antibodies (ADA) and secondary nonresponse as well as injection site and infusion reactions. The clinical usefulness of measuring ADA hinges on whether test results inform management changes, thereby leading to improved outcomes, compared with management directed by symptoms, clinical assessment, and standard laboratory evaluation. Limited evidence has described management changes after measuring ADA. A small RCT in patients with Crohn disease comparing ATI-informed management of relapse with standard dose escalation did not demonstrate improved outcomes with the ATI-informed approach. Additionally, many assays—some having significant limitations—have been used in studies; ADA threshold values that are informative for discriminating treatment responses have not been established. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have ulcerative colitis (UC) or Crohn's disease (CD) receiving vedolizumab or ustekinumab, there is an interest in monitoring this therapy not only for the purpose of identifying markers that will serve as end points for successful treatment, but also for timely cessation or switching of therapy in those unlikely to respond. However, based on the peer reviewed medical literature further randomized controlled trials are needed to investigate the efficacy of proposed preventative and management algorithms regarding antidrug antibodies (ADA) testing. Currently there are no society guidelines that include recommendations for ADA testing. More controlled data is needed to define the best cut-off to define abnormal values of the measured monitor parameters, define optimal thresholds for the different interventions and the subpopulations as to who will benefit the most from this testing. The evidence is insufficient to determine the effects of the technology on net health outcomes. .

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: No specific code. Per manufacturer, these tests will be reported with 1 unit of 84999

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Ordas I, Mould DR, Feagan BG et al. Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. *Clin Pharmacol Ther* 2012; 91(4):635-46.

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Lee LY, Sanderson JD, Irving PM. Anti-infliximab antibodies in inflammatory bowel disease: prevalence, infusion reactions, immunosuppression and response, a meta-analysis. *Eur J Gastroenterol Hepatol* 2012 [Epub ahead of print].

Afif W, Loftus EV, Jr., Faubion WA et al. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. *Am J Gastroenterol* 2010; 105(5):1133-9.

Steenholdt C, Bendtzen K, Brynskov J et al. Cut-off levels and diagnostic accuracy of infliximab trough levels and anti-infliximab antibodies in Crohn's disease. *Scand J Gastroenterol* 2011; 46(3):310-8.

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Finckh A, Dudler J, Wermelinger F et al. Influence of anti-infliximab antibodies and residual infliximab concentrations on the occurrence of acquired drug resistance to infliximab in rheumatoid arthritis patients. *Joint Bone Spine* 2010; 77(4):313-8.

Bendtzen K, Geborek P, Svenson M et al. Individualized monitoring of drug bioavailability and immunogenicity in rheumatoid arthritis patients treated with the tumor necrosis factor alpha inhibitor infliximab. *Arthritis Rheum* 2006; 54(12):3782-9.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.84, 8/9/2012

Specialty Matched Consultant Advisory Panel 2/2013

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.84, 9/12/13

Specialty Matched Consultant Advisory Panel 2/2014

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.84, 10/9/14

Specialty Matched Consultant Advisory Panel 2/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.84, 11/12/15

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.84, 11/10/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.84, 11/9/2017

Specialty Matched Consultant Advisory Panel 2/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.84, 11/8/2018

Policy Implementation/Update Information

For Policy Named: Measurement of Serum Antibodies to Infliximab

10/1/12 New policy. Measurement of antibodies to infliximab in a patient receiving treatment with infliximab, either alone or as a combination test which includes the measurement of serum infliximab levels, is considered **investigational**. Medical director review 9/18/2012.

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Notification given 10/1/12. Policy effective 1/1/13. (lpr)

3/12/13 Specialty Matched Consultant Advisory panel review meeting 2/20/2013. No change to policy statement. (lpr)

For Policy Renamed: Measurement of Serum Antibodies to Infliximab and Adalimumab

11/12/13 Policy title changed to add “Adalimumab”. Added the following statement to the “When Not Covered” section: Measurement of antibodies to adalimumab in a patient receiving treatment with adalimumab, either alone or as a combination test which includes the measurement of serum adalimumab levels, is considered investigational. Revised Description section. Reference added. Medical director review 10/2013. (lpr)

3/11/14 Specialty matched consultant advisory panel review meeting 2/25/2014. No change to policy statement. (lpr)

11/11/14 Reference added. No change to policy statement. (lpr)

3/10/15 Specialty matched consultant advisory panel review meeting 2/25/2015. No change to policy statement. (lpr)

4/1/16 Description section updated. Reference added. Specialty matched consultant advisory panel review meeting 2/24/2016. (an)

3/31/17 Updated Policy Guidelines section. Specialty Matched Consultant Advisory Panel review meeting 2/22/2017. No change to policy statement. (an)

12/15/17 Updated Description section to add information regarding vedolizumab and the Anser VDZ test. The following added to Policy statement: **Measurement of serum antibodies to vedolizumab is considered investigational for all applications.** Policy Guidelines and References updated. (an)

3/29/18 Specialty Matched Consultant Advisory Panel review 2/28/2018. No change to policy statement. (an)

4/27/18 Updated Description section to correctly define vedolizumab as an integrin receptor antagonist for clarity. Reference added. No change to policy intent. (krc)

9/28/18 Updated Description section to add information regarding ustekinumab and the Anser UST test. The following added to Policy statement: **Measurement of serum antibodies to ustekinumab is considered investigational for all applications.** Policy Guidelines updated. (krc)

3/12/19 Policy title changed to add “Vedolizumab” and “Ustekinumab”. Reference added. Specialty Matched Consultant Advisory Panel review 2/20/2019. No change to policy statement. (an)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational

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purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.