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

Introduction

Antibodies are a specific type of protein. They are made by the body’s immune system. Antibodies help fight germs and other substances inside the body that the immune system sees as harmful. The immune system custom-creates each type of antibody to fight what it sees as invading and destructive things. However, the body can also make antibodies to fight drugs that are intended to treat specific diseases. Blood tests have been developed that try to look at whether a person’s body has developed antibodies to the drugs Remicade® (infliximab), Humira® (adalimumab), Entyvio® (vedolizumab), and Stelara® (ustekinumab). These blood tests are investigational (unproven). Medical studies so far have not shown that changes in treatment based on the results of these blood tests have improved health results. More and larger studies are needed to show if and how well these types of blood tests work.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
# Policy Coverage Criteria

## Drug

**Remicade® (infliximab)**

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

**Humira® (adalimumab)**

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

**Entyvio® (vedolizumab)**

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

**Stelara® (ustekinumab)**

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

## Coding

According to materials from Prometheus Laboratories on Anser™IFX, Anser™ADA, Anser™ VDZ, and Anser UST™ these tests will be reported using 1 unit of the following CPT code:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>Unlisted Chemistry Procedure</td>
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</table>

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Evidence Review

Description

Infliximab (Remicade) is an intravenous tumor necrosis factor α blocking agent approved by the U.S. Food and Drug Administration for the treatment of rheumatoid arthritis, Crohn disease, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and ulcerative colitis. Adalimumab (Humira) is a subcutaneous tumor necrosis factor α inhibitor that is approved by the Food and Drug Administration for the treatment of Crohn disease and ulcerative colitis in adults only and juvenile idiopathic arthritis. Following the primary response to infliximab and adalimumab, some patients become secondary nonresponders. The development of antidrug antibodies (ADA) is considered a cause of this secondary nonresponse.

Background

Infliximab and Adalimumab in Autoimmune Diseases

Infliximab is a chimeric (mouse/human) anti-tumor necrosis factor α (TNF-α) monoclonal antibody. Adalimumab is a fully human monoclonal antibody to TNF-α. Use of monoclonal antibodies has revolutionized therapy for patients with inflammatory diseases such as inflammatory bowel disease (eg, Crohn disease, ulcerative colitis), 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. It is estimated that 1 out of 3 patients do not respond to induction therapy (primary nonresponse); further, among initial responders, response wanes over time in approximately 20% to 60% of patients (secondary nonresponse). The reasons for therapeutic failures remain a matter of debate but include accelerated drug clearance (pharmacokinetics) and neutralizing agent activity (pharmacodynamics) due to antidrug antibodies (ADA). ADA are also associated with injection-site reactions (adalimumab) and acute infusion reactions and delayed hypersensitivity
reactions (infliximab). As a fully human antibody, adalimumab is considered less immunogenic than chimeric antibodies like infliximab.

**Detection of ADA**

The detection and quantitative measurement of ADA is difficult, owing to drug interference and identifying when antibodies likely have a neutralizing effect. First-generation assays, (ie, enzyme-linked immunosorbent assays [ELISA]) can measure only ADA in the absence of detectable drug levels, due to interference of the drug with the assay. Other techniques available for measuring antibodies include the radioimmunoassay method, and more recently, the homogenous mobility shift assay using high-performance liquid chromatography. Disadvantages of the radioimmunoassay method are associated with the complexity of the test and prolonged incubation time, along with safety concerns related to the handling of radioactive material. The homogenous mobility shift assay measures ADA when infliximab is present in the serum. Studies evaluating the validation of results among different assays are lacking, making interstudy comparisons difficult. One retrospective study by Kopylov et al (2012), which evaluated 63 patients, demonstrated comparable diagnostic accuracy between 2 different ELISA methods in patients with inflammatory bowel disease (ie, double-antigen ELISA and antihuman lambda chain-based ELISA.) This study did not include an objective clinical and endoscopic scoring system for validation of results.

**Detection of Vedolizumab (VDZ)**

Vedolizumab (Entyvio) is an intravenous tumor necrosis factor blocking agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of adult ulcerative colitis (UC) and adult Crohn’s disease (CD). Vedolizumab is generally given for those patients who have had an inadequate response with, lost response to, or were intolerant to tumor necrosis factor (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.

Serum concentrations of vedolizumab (VDZ) may vary among equally dosed patients which can affect patient outcomes. Some patients may develop immunogenicity (non-response) to VDZ by producing antibodies to vedolizumab and the presence of persistent anti-vedolizumab antibody has been observed to reduce serum concentrations of vedolizumab. 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.

**Detection of Ustekinumab**

Chiu (2015) reports on clinical outcomes of a prospective case series involving 76 subjects with plaque psoriasis treated with ustekinumab for a minimum of 7 months. Antibodies to ustekinumab were detected in 5 (6.6%) subjects after a mean of 13 months of treatment. These subjects were found to have significantly lower serum ustekinumab concentrations (0.01 mg/L vs. 0.2 mg/L, p<0.001). Responders had higher trough levels than non-responders (0.6 mg/ml vs 0.07 mg/ml, p=0.03). Subjects with antibodies to ustekinumab detected vs. those without antibodies to ustekinumab (0% vs. 69%, p=0.004) reported lower Psoriasis Area and Severity Index (PASI 50) scores. There were also no significant differences in the percentage of antibodies to ustekinumab formation between subjects with or without antibodies to adalimumab who had failed previous adalimumab (14.3 % vs. 12.5%, p=1.00) noted.

**Treatment Options for Secondary Nonresponse to Anti-TNF therapy**

A diminished or suboptimal response to infliximab, adalimumab, or vedolizumab 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.

**Summary of Evidence**

For individuals who have rheumatoid arthritis, psoriatic arthritis, or juvenile idiopathic arthritis; inflammatory bowel disease (eg, Crohn disease, ulcerative colitis); ankylosing spondylitis; or plaque psoriasis who receive evaluation for anti-TNF-α inhibitor ATI or to ATA, the evidence includes multiple systematic reviews, a randomized controlled trial, and observational studies. Relevant outcomes are test validity, change in disease status, health status measures, quality of life, and treatment-related morbidity. ATI or 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 ADA and secondary nonresponse as well as injection-site and infusion-site 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 randomized controlled trial 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, 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.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 1.

**Table 1. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td><strong>Ongoing</strong></td>
<td>A Randomized, Multi-Center Biomarker Trial to Predict Therapeutic Responses of Patients With Rheumatoid Arthritis to a Specific Biologic Mode of Action</td>
<td>200</td>
<td>Jun 2018 (ongoing)</td>
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<tr>
<td><strong>Unpublished</strong></td>
<td>Comparative Analysis of Two Therapeutic Strategies in Patients With Spondyloarthritis Treated With Anti-TNF Biologics (STRADA)</td>
<td>104</td>
<td>Apr 2017 (terminated)</td>
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<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
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<tr>
<td>NCT01895764</td>
<td>Effect of the Combination of Methotrexate and Adalimumab on Reduction of Immunization in Ankylosing Spondylitis (COMARIS)</td>
<td>110</td>
<td>Apr 2015 (completed)</td>
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NCT: national clinical trial

Practice Guidelines and Position Statements

American College of Gastroenterology Institute

The American College of Gastroenterology Institute (2017) published guidelines on therapeutic drug monitoring in inflammatory bowel disease. The guidelines note that:

When anti-drug antibodies are detected, it is unclear what antibody level is clinically meaningful…. the reporting of anti-drug antibodies is variable between commercial assays, with some assays being very sensitive for detecting very-low-titer antibodies of limited clinical significance. Uniform thresholds for clinically relevant antibody titers are lacking. At this time, it is unclear how antibodies affect drug efficacy when both active drug and antibodies are detected. In cases of low trough concentrations and low or high anti-drug antibodies, the evidence to clarify optimal management is lacking.

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (2016) issued guidance on therapeutic monitoring of tumor necrosis factor α inhibitors in the treatment of patients with Crohn disease. The Institute recommended that laboratories monitoring tumor necrosis factor α inhibitors in patients with Crohn disease who have lost response to the treatment should “work with clinicians to collect data through a prospective study, for local audit, or for submission to an existing registry.”

Medicare National Coverage

There is no national coverage determination.
Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Prometheus Laboratories, a College of American Pathologists-accredited lab under the Clinical Laboratory Improvement Amendments, offers non-radio-labeled, fluid-phase homogenous mobility shift assay tests called Anser™IFX (for infliximab), Anser™ADA (for adalimumab), and Anser™ VDZ for vedolizumab. These tests are not based on an ELISA test, and each can measure ADA in the presence of detectable drug levels, improving on a major limitation of the ELISA method. Both Anser™IFX and Anser™ADA tests measure serum drug concentrations and ADA.

References


32. Raine, T. Vedolizumab for inflammatory bowel disease:: Changing the game, or more of the same? United European Gastroenterology 2014 Vol 2 (5) 333-344


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**History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
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<tr>
<td>02/01/19</td>
<td>New policy, approved January 4, 2019. This policy replaces policy 2.04.84. Policy created with literature review through September 2018. Measurement of antibodies to infliximab, adalimumab, vedolizumab, and ustekinumab is considered investigational.</td>
</tr>
<tr>
<td>04/01/19</td>
<td>Interim Review, approved March 12, 2019. Reference 36 added. Added criteria to policy statement for ustekinumab test, Anser™ UST as investigational. Title changed from “Measurement of Serum Antibodies to Infliximab, Adalimumab, and Vedolizumab” to “Measurement of Serum Antibodies to Infliximab, Adalimumab, Vedolizumab, and Ustekinumab”. History section updated.</td>
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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
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