Medical Coverage Policy | Measurement of Serum Antibodies to Infliximab and Adalimumab

EFFECTIVE DATE: 10|02|2012
POLICY LAST UPDATED: 09|03|2019

OVERVIEW
This policy documents secondary loss of response to infliximab and adalimumab as seen in a certain percentage of patients; the development of anti-drug antibodies has been suggested as one reason for nonresponse.

MEDICAL CRITERIA
Not applicable

PRIOR AUTHORIZATION
Not applicable

POLICY STATEMENT
BlueCHiP for Medicare
Measurement of antibodies to infliximab or adalimumab in a patient receiving treatment with infliximab or adalimumab, either alone or as a combination test that includes the measurement of serum infliximab levels or serum adalimumab levels is not covered as the evidence is insufficient to determine the effects of the technology on health outcomes.

Commercial Products
Measurement of antibodies to infliximab or adalimumab in a patient receiving treatment with infliximab or adalimumab, either alone or as a combination test that includes the measurement of serum infliximab levels or serum adalimumab levels is considered not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes.

COVERAGE
Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable not medically necessary/not covered benefits/coverage.

BACKGROUND
Infliximab (Remicade®) is an intravenous tumor necrosis factor (TNF) á-blocking agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis (RA), Crohn disease (CD), ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and ulcerative colitis. Adalimumab (Humira®), is a subcutaneous TNF-á inhibitor that is FDA approved for 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.

Infliximab and Adalimumab in autoimmune disease
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. Therapy with monoclonal antibodies has revolutionized therapy in patients with inflammatory diseases such as inflammatory bowel disease ([IBD], 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 antidrug antibodies:
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, (i.e., 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 (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 homogenous mobility shift assay measures ADA when infliximab is present in 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.

Treatment options for patients with secondary loss of response to anti-TNF therapy:
A diminished or suboptimal response to infliximab or adalimumab 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.

Regulatory Status
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories that offer LDTs must be licensed by the CLIA for high-complexity testing. To date, the FDA 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) and Anser™ADA (for adalimumab). Neither is 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 tests measure serum drug concentrations and ADA.

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.

CODING

BlueCHiP for Medicare and Commercial Products:

At this time a code has not been assigned for the measurement of serum antibodies to infliximab or adalimumab; therefore the following unlisted code should be used:

84999 Unlisted chemistry procedure

RELATED POLICIES

None

PUBLISHED

Provider Update, November 2019
Provider Update, Nov. /Dec. 2018
Provider Update, July 2017
Provider Update, December 2016
Provider Update, February 2016
Provider Update, January 2015

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