Medical Coverage Policy | Measurement of Serum Antibodies to Selected Biologic Agents

EFFECTIVE DATE: 01|01|2020
POLICY LAST UPDATED: 01|07|2020

OVERVIEW

Infliximab (Remicade) is an intravenous tumor necrosis factor α blocking agent approved by the U.S. Food and Drug Administration (FDA) 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 FDA approved for the treatment of Crohn's disease and ulcerative colitis in adults and those with juvenile idiopathic arthritis. Vedolizumab (Entyvio) is an intravenous integrin receptor antagonist that is FDA approved for treatment of ulcerative colitis and Crohn's Disease in adults. Ustekinumab (Stelara) is an intravenous and subcutaneous human interleukin-12 and -23 antagonist that is FDA approved for the treatment of psoriatic psoriasis, Crohn's disease, and ulcerative colitis in adults, and plaque psoriasis in adolescents and adults. Following the primary response to these medications, some patients become secondary nonresponders. The development of antidrug antibodies is considered a cause of this secondary nonresponse.

Currently FDA approved TNF blocking agents include infliximab, adalimumab, vedolizumab, and ustekinumab.

MEDICAL CRITERIA

Not applicable

PRIOR AUTHORIZATION

Not applicable

POLICY STATEMENT

BlueCHiP for Medicare

Measurement of antibodies to tumor necrosis factor (TNF) blocking agents in a patient receiving treatment with a TNF blocking agent, either alone or as a combination test, which includes the measurement of serum TNF blocking agent 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 tumor necrosis factor (TNF) blocking agents in a patient receiving treatment with a TNF blocking agent, either alone or as a combination test, which includes the measurement of serum TNF blocking agent levels, is 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 Evidence of Coverage or Subscriber Agreement for applicable not medically necessary/not covered benefits/coverage.

BACKGROUND

Infliximab, Adalimumab, Vedolizumab, and Ustekinumab in Autoimmune Diseases

Tumor necrosis factor (TNF) inhibitors (e.g. infliximab, adalimumab, vedolizumab, or ustekinumab) are used to treat multiple inflammatory conditions, including rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis; inflammatory bowel disease (eg, Crohn disease, ulcerative colitis), ankylosing spondylitis, and plaque psoriasis. These agents are generally given to patients who fail conventional medical therapy, and they are

typically highly effective for the 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 in 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 is also associated with injection-site reactions and acute infusion reactions and delayed hypersensitivity reactions.

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 the 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 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 Secondary Nonresponse 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 a 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 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 four non-radio-labeled, fluid-phase homogenous mobility shift assay tests: called Anser IFX (for infliximab), Anser ADA (for adalimumab), Anser VDZ (for vedolizumab), and Anser UST (for ustekinumab). The tests measure both serum drug concentrations and ADA. They are not based on an ELISA test, and can measure ADA in the presence of detectable drug levels, improving on a major limitation of the ELISA method.

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-tumor necrosis factor α inhibitor antibodies to infliximab, adalimumab,vedolizumab, or ustekinumab, the evidence includes multiple systematic reviews, a randomized controlled trial, and observational studies. The relevant outcomes are test validity, change in disease status, health status measures, quality of life, and treatment-related morbidity. ATI or antibodies to adalimumab 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's 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

The following services are considered not covered for BlueCHiP for Medicare and not medically necessary for Commercial products:

80145 Adalimumab (effective 1/1/2020)
80230 Infliximab (effective 1/1/2020)
80280 Vedolizumab (effective 1/1/2020)

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

84999 Unlisted chemistry procedure

RELATED POLICIES

None

PUBLISHED

Provider Update, March 2020
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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