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OVERVIEW

Biologic agents used to treat autoimmune diseases include infliximab, adalimumab, vedolizumab, and ustekinumab. 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's 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 U.S. Food and Drug Administration approved biologic agents include infliximab, adalimumab, vedolizumab, and ustekinumab.

MEDICAL CRITERIA

Not applicable

PRIOR AUTHORIZATION

Not applicable

POLICY STATEMENT

Medicare Advantage Plans

Measurement of antidrug antibodies in a patient receiving treatment with a biologic 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 antidrug antibodies in a patient receiving treatment with a biologic 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

Biologic agents (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 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 (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 Biologic Agents

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 biologic agent (in patients who continue to have a loss of response after receiving the increased dose), or switching to a non-biologic 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 serum antibodies to infliximab, adalimumab, vedolizumab, or ustekinumab, 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. Antibodies to biologic agents 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 and secondary nonresponse as well as injection-site and infusion-site reactions. The clinical usefulness of measuring antidrug antibodies 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 antidrug antibodies. A small randomized controlled trial in patients with Crohn's disease comparing antidrug -informed management of relapse with standard dose escalation did not demonstrate improved outcomes with the antidrug antibody -informed approach. Additionally, many assays, some having significant limitations, have been used in studies; antidrug antibody 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 Medicare Advantage Plans and not medically necessary for Commercial products:

- 80145** Adalimumab
- 80230** Infliximab
- 80280** Vedolizumab

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 2021
- 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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