Protocol

Measurement of Serum Antibodies to Selected Biologic Agents

(20484)

(Formerly Measurement of Serum Antibodies to Infliximab and Adalimumab)

Medical Benefit		**Effective Date**: 06/01/20	**Next Review Date**: 03/21
Preauthorization	No	**Review Dates**: 11/14, 11/15, 11/16, 03/17, 03/18, 03/19, 03/20	

This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With rheumatoid, psoriatic, or juvenile idiopathic arthritis; inflammatory bowel disease; ankylosing spondylitis; psoriasis	Interventions of interest are: • Evaluation for anti-tumor necrosis factor α inhibitor antibodies to infliximab or adalimumab	Comparators of interest are: • Standard of care	Relevant outcomes include: • Test validity • Change in disease status • Health status measures • Quality of life • Treatment-related morbidity

DESCRIPTION

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.

SUMMARY OF EVIDENCE

For individuals who have rheumatoid arthritis, psoriatic arthritis, or juvenile idiopathic arthritis; inflammatory bowel disease (e.g., 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 observa-

tional 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.

POLICY

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 considered **investigational.**

POLICY GUIDELINES

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

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 (e.g., 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 one in three 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).[1] 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 (i.e., 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 two different ELISA methods in patients with inflammatory bowel disease(i.e., double-antigen ELISA and antihuman lambda chain-based ELISA).[2] 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.

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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