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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 and 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 there is insufficient peer-reviewed scientific literature that demonstrates that the service is effective.

COVERAGE

Benefits may vary between groups/contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for limitations of benefits/coverage when services are not medically necessary.

BACKGROUND

Infliximab (Remicade[®], Janssen Biotech) is an intravenous tumor necrosis factor (TNF) α -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[®], AbbVie) is a subcutaneous TNF- α inhibitor that is FDA approved for treatment of these indications (CD and ulcerative colitis [UC] in adults only) and juvenile idiopathic arthritis. Following primary response to infliximab and adalimumab, some patients become nonresponders (secondary nonresponse). The development of antidrug antibodies is considered to be a cause of 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. An estimated one-third of patients do not respond to induction therapy (primary nonresponse), and among initial responders, response wanes over time in approximately 20% to 60% of patients (secondary nonresponse). The reasons for therapeutic failures remains a matter of debate but include accelerate drug clearance (pharmacokinetics) and neutralizing agent activity (pharmacodynamics) due to

ADA. ADA are also associated with acute infusion reactions (infliximab), injection site reactions (adalimumab), and delayed hypersensitivity reactions (infliximab). As a fully human antibody, adalimumab is considered less immunogenic than chimeric antibodies, such as infliximab.

Detection of antidrug antibodies:

The detection and quantitative measurement of ADA has been fraught with difficulty 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 HMSA has the advantage of being able to measure 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 in 63 patients demonstrated comparable diagnostic accuracy between 2 different ELISA methods in patients with IBD, i.e., double antigen ELISA and antihuman lambda chain ELISA.² 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 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 CLIA, offers nonradiolabeled, fluid-phase HMSA tests called Anser[™]IFX for infliximab and Anser[™]ADA for adalimumab. Neither test is based on an ELISA and each can measure antidrug antibodies in the presence of detectable drug levels, improving on a major limitation of the ELISA method. Both tests measure serum drug concentrations and antidrug antibodies.

The evidence for measuring anti-TNF- α inhibitor antibodies in patients who have rheumatoid arthritis, psoriatic arthritis, or juvenile idiopathic arthritis; inflammatory bowel diseases (Crohn disease, ulcerative colitis); ankylosing spondylitis; or plaque psoriasis includes multiple systematic reviews, a single randomized controlled trial, and other observational studies. Relevant outcomes are test accuracy and validity, change in disease status, health status measures, quality of life, and treatment-related morbidity.

Antibodies-to-infliximab (ATI) or to adalimumab (ATA) develop in a substantial proportion of treated patients and are believed to neutralize or enhance clearance of the drugs. Considerable evidence demonstrates an association between ADA and secondary nonresponse as well as injection site and infusion 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 describes management changes after measuring ADA. A small, randomized controlled trial in patients with CD comparing ATI-informed management of relapse with standard dose escalation did not demonstrate improved outcomes with the ATI-informed approach. Additionally, many different 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. Therefore, the measurement of antibodies to infliximab in a patient receiving treatment with infliximab is considered not medically necessary and the measurement of antibodies to adalimumab in a patient receiving treatment with adalimumab is considered not medically necessary as there is no proven efficacy.

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

RELATED POLICIES

None

PUBLISHED

Provider Update, December 2016

Provider Update, February 2016

Provider Update, January 2015

Provider Update, January 2014

Provider Update, December 2012

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