

EFFECTIVE DATE: 10|02|2012

POLICY LAST UPDATED: 05|16|2017

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 the evidence is insufficient to determine the effects of the technology on health outcomes.

COVERAGE

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

BACKGROUND

Infliximab (Remicade[®]) 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[®]) is a subcutaneous TNF- α inhibitor that is FDA approved for treatment of Crohn disease and ulcerative colitis in adults only and juvenile idiopathic arthritis. Following primary response to infliximab and adalimumab, some patients become secondary nonresponders. The development of antidrug antibodies (ADA) is considered to be 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. 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 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 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. 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 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 enzyme-linked immunosorbent assay (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.

For individuals who have rheumatoid arthritis, psoriatic arthritis, or juvenile idiopathic arthritis; inflammatory bowel disease (Crohn disease, ulcerative colitis); ankylosing spondylitis; or plaque psoriasis who receive evaluation for anti-tumor necrosis factor α inhibitor antibodies to infliximab or adalimumab, the evidence includes multiple systematic reviews, 1 randomized controlled trial (RCT), and 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 has demonstrated an association between antidrug antibodies (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 has described management changes after measuring ADA. A small RCT 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. Therefore, this service is considered not medically necessary for BlueCHiP for Medicare and Commercial products.

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, July 2017

Provider Update, December 2016

Provider Update, February 2016

Provider Update, January 2015

Provider Update, January 2014

Provider Update, December 2012

REFERENCES

1. Bendtzen K. Personalized medicine: theranostics (therapeutics diagnostics) essential for rational use of tumor necrosis factor-alpha antagonists. *Discov Med.* Apr 2013;15(83):201-11. PMID 23636137
2. Kopylov U, Mazor Y, Yavzori M et al. Clinical utility of antihuman lambda chain-based enzyme-linked immunosorbent assay (ELISA) versus double antigen ELISA for the detection of anti-infliximab antibodies. *Inflammatory bowel diseases* 2012; 18(9):1628-33.
3. Wang SL, Ohrmund L, Hauenstein S et al. Development and validation of a homogeneous mobility shift assay for the measurement of infliximab and antibodies-to-infliximab levels in patient serum. *J Immunol Methods* 2012; 382(1-2):177-88.
4. Steenholdt C, Bendtzen K, Brynskov J, et al. Clinical implications of measuring drug and anti-drug antibodies by different assays when optimizing infliximab treatment failure in Crohn's disease: post hoc analysis of a randomized controlled trial. *Am J Gastroenterol.* Jul 2014; 109(7):1055-1064. PMID 24796769
5. Steenholdt C, Brynskov J, Thomsen OO, et al. Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. *Gut.* Jun 2014; 63(6):919-927. PMID 23878167
6. Nanda KS, Cheifetz AS, Moss AC. Impact of antibodies to infliximab on clinical outcomes and serum infliximab levels in patients with inflammatory bowel disease (IBD): a meta-analysis. *The American journal of gastroenterology* 2013; 108(1):40-7; quiz 48.
7. Wang SL, Hauenstein S, Ohrmund L et al. Monitoring of adalimumab and antibodies-to-adalimumab levels in patient serum by the homogeneous mobility shift assay. *Journal of pharmaceutical and biomedical analysis* 2013; 78-79:39-44.
8. Meroni PL, Valentini G, Ayala F, et al. New strategies to address the pharmacodynamics and pharmacokinetics of tumor necrosis factor (TNF) inhibitors: A systematic analysis. *Autoimmun Rev.* Sep 2015; 14(9):812-29. PMID 25985765
9. White CM, Ip S, McPheeters M, et al. Using existing systematic reviews to replace de novo processes in conducting comparative effectiveness reviews methods guide for effectiveness and comparative effectiveness reviews. Rockville MD 2008.

10. Afif W, Loftus EV, Jr., Faubion WA et al. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. The American journal of gastroenterology 2010; 105(5):1133-9.

11. Hernandez-Breijs B, Chaparro M, Cano-Martinez D, et al. Standardization of the homogeneous mobility shift assay protocol for evaluation of anti-infliximab antibodies. Application of the method to Crohn's disease patients treated with infliximab. Biochem Pharmacol. Sep 21 2016. PMID 27664854

12. National Institute for Health and Care Excellence (NICE). Therapeutic monitoring of TNF-alpha inhibitors in Crohn's disease (LISA-TRACKER ELISA kits, IDKmonitor ELISA kits, and Promonitor ELISA kits [DG22]. <https://www.nice.org.uk/guidance/dg22/chapter/1-Recommendations>. Accessed October 31, 2016

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