Medical Coverage Policy | Measurement of Serum Antibodies to Infliximab and Adalimumab

EFFECTIVE DATE: 10/02/2012
POLICY LAST UPDATED: 11/18/2014

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.

PRIOR AUTHORIZATION

Not Applicable

POLICY STATEMENT

BlueCHiP for Medicare and Commercial

Measurement of antibodies to infliximab or adalimumab in a patient receiving treatment with infliximab or adalimumab, either alone or as a combination test which 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 procedure/service is effective.

MEDICAL CRITERIA

None

BACKGROUND

Infliximab (Remicade® Janssen Biotech) is an intravenous tumor necrosis factor (TNF) alpha 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® AbbVie) is a subcutaneous TNF alpha inhibitor that is FDA-approved for treatment of the above indications (Crohn's disease and ulcerative colitis in adults only) plus juvenile idiopathic arthritis. Secondary loss of response to infliximab and adalimumab is seen in a certain percentage of patients; the development of anti-drug antibodies has been suggested as one reason for nonresponse.

Antibodies-to-infliximab (ATI) or to adalimumab (ATA) are present in a substantial number of patients treated with infliximab or adalimumab, respectively, and there may be a correlation between the level of these antibodies and clinical response. However, the clinical utility of measuring antidrug antibody concentrations has not been established, as it is unknown how patient management would change based on test results. Limited evidence describes changes in management after measurement of ATI, but does not compare these management changes with those made in the absence of ATI measurement. One randomized controlled trial that compared ATI-informed management of relapse with standard dose escalation did not demonstrate benefit with the ATI approach. Additionally, technical factors related to different assay methods are unresolved, and ATI or ATA threshold values that are informative for discriminating treatment response have not been definitively established.

Infliximab and Adalimumab in autoimmune disease

Infliximab is a chimeric (mouse/human) anti-tumor necrosis factor (TNF)-alpha monoclonal antibody. Adalimumab is a fully human monoclonal antibody to TNF-alpha. Therapy with monoclonal antibodies has revolutionized therapy in patients with immune diseases such as inflammatory bowel disease (Crohn's disease

[CD] and ulcerative colitis [UC]), 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 reason for therapeutic failures remains a matter of debate. One proposed factor associated with loss of response is the production of antidrug antibodies, which accelerate clearance of the drug. (1) Antidrug antibodies also have been associated with acute infusion reactions (both drugs) and with delayed hypersensitivity reactions. 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 antidrug antibodies, has been fraught with difficulty. First-generation assays, (i.e., enzyme-linked immunosorbent assays [ELISA]) can only measure antidrug antibodies in the absence of detectable drug levels due to interference of the drug with the assay, limiting clinical utility. 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 antidrug antibodies when infliximab is present in the serum. Studies evaluating the validation of the results between different assays are lacking, making interstudy comparisons difficult. One retrospective study in 63 patients demonstrated comparable diagnostic accuracy between 2 different ELISA methods, 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.

Prometheus® Laboratories Inc. offers nonradiolabeled, fluid-phase HMSA tests called Anser™IFX for infliximab and Anser™ADA for adalimumab. Neither test is ELISA-based, nor can each measure antidrug antibodies in the presence of detectable drug levels, improving upon a major limitation of the ELISA method. Both tests measure serum drug concentrations and antidrug antibodies to infliximab. These tests were developed and their performance characteristics determined by Prometheus Laboratories Inc. Neither has been cleared or approved by the U.S. Food and Drug Administration.

Antibodies-to-infliximab (ATI) or to adalimumab (ATA) are present in a substantial number of patients treated with infliximab or adalimumab, respectively, and there may be a correlation between the level of these antibodies and clinical response. However, the clinical utility of measuring antidrug antibody concentrations has not been established, as it is unknown how patient management would change based on test results. Limited evidence describes changes in management after measurement of ATI, but does not compare these management changes with those made in the absence of ATI measurement. One RCT that compared ATI-informed management of relapse with standard dose escalation did not demonstrate benefit with the ATI approach. Additionally, technical factors related to different assay methods are unresolved, and ATI or ATA threshold values that are informative for discriminating treatment response have not been definitively established. 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.

COVERAGE

Benefits may vary between groups/contracts. Please refer to the appropriate Evidence of Coverage or Subscriber Agreement for applicable Services Not Medically Necessary coverage/benefits.

CODING

BlueCHiP for Medicare and Commercial

At this time a code has not been assigned to the measurement of serum antibodies to infliximab or adalimumab, therefore the following unlisted CPT code should be used:

84999

RELATED POLICIES

None

PUBLISHED

Provider Update	Jan 2015
Provider Update	Jan 2014
Provider Update	Dec 2012

REFERENCES

1. Ordas I, Mould DR, Feagan BG et al. Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. Clin Pharmacol Ther 2012; 91(4):635-46.

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. Cassinotti A, Travis S. Incidence and clinical significance of immunogenicity to infliximab in Crohn's disease: a critical systematic review. Inflammatory bowel diseases 2009; 15(8):1264-75.

7. Lee LY, Sanderson JD, Irving PM. Anti-infliximab antibodies in inflammatory bowel disease: prevalence, infusion reactions, immunosuppression and response, a meta-analysis. Eur J Gastroenterol Hepatol 2012.

8. 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.

9. Plasencia C, Pascual-Salcedo D, Nuno L et al. Influence of immunogenicity on the efficacy of longterm treatment of spondyloarthritis with infliximab. Annals of the rheumatic diseases 2012; 71(12):1955-60.

10. 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.

11.. Korswagen LA, Bartelds GM, Krieckaert CL et al. Venous and arterial thromboembolic events in adalimumab-treated patients with antiadalimumab antibodies: a case series and cohort study. Arthritis and rheumatism 2011; 63(4):877-83

12. Masson PL. Thromboembolic events and anti-tumor necrosis factor therapies. International immunopharmacology 2012; 14(4):444-5.

13. Bartelds GM, Krieckaert CM, Nurmohamed MT et al. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. JAMA 2011; 305(14):1460-68.

14. Garces S, Demengeot J, Benito-Garcia E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. Annals of the rheumatic diseases 2012

15. 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.