

MEDICAL POLICY



MEDICAL POLICY DETAILS	
Title	MEASUREMENT OF SERUM ANTIBODIES TO INFlixIMAB, ADALIMUMAB, AND VEDOLIZUMAB
Policy Number	2.02.47
Category	Technology Assessment
Effective Date	12/17/15
Revised Date	12/15/16, 12/21/17
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Product Disclaimer	<ul style="list-style-type: none"> • <i>If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.</i> • <i>If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.</i> • <i>If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.</i>

POLICY STATEMENT

- I. Based upon our criteria and assessment of peer-reviewed literature, measurement of antibodies to infliximab in a patient receiving treatment with infliximab, either alone or as a combination test which includes the measurement of serum infliximab levels, is considered **investigational**.
- II. Based upon our criteria and assessment of peer-reviewed literature, measurement of antibodies to adalimumab in a patient receiving treatment with adalimumab, either alone or as a combination test which includes the measurement of serum adalimumab levels, is considered **investigational**.
- III. Based upon our criteria and assessment of peer-reviewed literature, measurement of antibodies to vedolizumab in a patient receiving treatment with vedolizumab, either alone or as a combination test which includes the measurement of serum adalimumab levels, is considered **investigational**.

POLICY GUIDELINES

- I. Prometheus® Laboratories Inc. offers nonradiolabeled, fluid-phase homogenous mobility shift assay (HMSA) tests called Anser™IFX for infliximab, Anser™ ADA for adalimumab, and Anser™VDZ. The three tests are not ELISA-based however each can measure antidrug antibodies in the presence of detectable drug levels, improving on a major limitation of the ELISA method. The tests measure serum drug concentrations and antidrug antibodies.
- II. These tests were developed and their performance characteristics determined by Prometheus Laboratories Inc. Neither has been cleared or approved by FDA.
- III. The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

DESCRIPTION

Anti-tumor necrosis factor- α (anti-TNF- α), infliximab (IFX) and adalimumab (ADA) are effective when there is insufficient control of disease with conventional treatment in patients with inflammatory disorders such as, inflammatory bowel disease (e.g., ulcerative colitis, Crohn's disease), rheumatoid arthritis (RA), and psoriatic arthritis, and ankylosing spondylitis. However up to 30% of patients do not respond to therapy and up to 60% that do respond to anti-TNF- α therapy lose response over time. Options for those who do not respond include increasing the dose interval, increase the dose, or change to another anti-TNF drug or to a drug from a different class. The reason for nonresponse or loss of

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response is unclear but may be due to formation of antibodies to anti-TNF agents. Antibodies to IFX (ATI), also called human antichimeric antibodies (HACAs), are reported to develop in up to approximately 60% of patients depending on the dosing schedule, administration of concurrent steroids or immunomodulators, and the method of measuring the antibodies in the blood. The antibodies can appear after the first IFX dose and can persist in the blood for up to 4.5 years after the drug is discontinued. The presence of antibodies has been associated with decreased concentration possibly from an accelerated clearance of the drug resulting in decreased efficacy. Antidrug antibodies have also been associated with acute infusion reactions and delayed hypersensitivity reactions. Adalimumab is considered less immunogenic compared to IFX because it is a fully human monoclonal antibody TNF- α while IFX is a chimeric (mouse/human) anti-TNF- α monoclonal antibody. Loss of clinical response of anti-TNF- α is a potential major limitation of this therapy leading to clinical relapse, impaired quality of life, and increased cost of care. Thus accurate monitoring of serum drug and anti-drug antibody levels has been suggested as part of anti-TNF therapy regimens.

Detection of drug and antibodies can be accomplished by enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA) and homogenous mobility shift assay (HMSA) however each method has disadvantages. ELISA can only measure antidrug antibodies in the absence of detectable drug levels. RIA is a complex test with prolong incubation time and safety concerns related to the handling of radioactive material. HMSA has the advantage of being able to measure antidrug antibodies when the drug is present in the serum. Technical factors related to different assay methods are unresolved making interstudy comparisons difficult and IFX or ADA antibody threshold values for each assay have not been established.

RATIONALE

Afif et al (2010) evaluated the clinical utility of measuring antibodies to infliximab (ATI) (referred to as human anti-chimeric antibodies [HACA] in the study) and infliximab concentrations by retrospectively reviewing the medical records of patients with IBD who had had ATI and infliximab concentrations measured. The study sought to determine whether these results affected clinical management. Medical record review from 2003 to 2008 identified 155 patients who had had ATI and infliximab concentrations measured and who met the study inclusion criteria. Seventy-two percent of the initial tests were ordered by a single physician. Clinical response to infliximab was retrospectively determined by the authors. Forty-seven percent of patients were on concurrent immunosuppressive medication. The main indications for testing were loss of response to infliximab (49%), partial response after initiation of infliximab (22%), and possible autoimmune/delayed hypersensitivity reaction (10%). ATI were identified in 35 patients (23%) and therapeutic infliximab concentrations in 51 patients (33%). Of 177 tests assessed, the results impacted treatment decisions in 73%. In ATI-positive patients, change to another anti-TNF agent was associated with a complete or partial response in 92% of patients, whereas dose escalation had a response of 17%. The authors concluded that measurement of ATI and infliximab concentration impacted management and was clinically useful. Increasing the infliximab dose in patients with ATI was ineffective, whereas in patients with subtherapeutic infliximab concentrations, this strategy was considered a good alternative to changing to another anti-TNF agent. Limitations to the study included its retrospective design and that the testing for antibodies to infliximab was performed using the ELISA testing method. Because there was no control group in this study, it is not possible to determine what changes in management would have been made in the absence of ATI measurement. Clinicians are likely to make some changes in management for patients who do not achieve or maintain a clinical response, and it is important to understand how these management decisions differ when ATI are measured.

Finckh et al (2010) tested whether the presence of antibodies to infliximab (ATI) and residual circulating infliximab levels prior to another infusion were associated with acquired infliximab resistance in RA. A multivariate logistic regression was used to analyze the relationship between ATI, residual infliximab concentrations, and acquired infliximab resistance in a nested cohort within a Swiss RA registry. Sixty-four RA patients on longstanding infliximab therapy were included; 24 had an acquired therapeutic resistance to infliximab, and 40 had continuous good response to infliximab. The two groups had similar disease characteristics, however, patients with acquired infliximab resistance required significantly higher dosages of infliximab and shorter infusion intervals than long-term good responders. The presence of residual infliximab tended to be associated with a decreased risk of acquired therapeutic resistance (odds ratio [OR], 0.4; 95% CI, 0.1 to 1.5),

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while the presence of ATIs tended to be associated with an increased risk of acquired therapeutic resistance (OR=1.8; 95% CI, 0.4 to 9.0). The presence of either high ATI levels or low residual infliximab concentrations was strongly associated with acquired therapeutic resistance to infliximab (OR=5.9; 95% CI, 1.3 to 26.6). However, just 42% of patients with acquired infliximab resistance had either low infliximab or high ATI levels. The authors concluded that their results suggested that the assessment of ATIs and residual infliximab levels is of limited value for individual patients in routine clinical care.

Lee et al (2012) conducted a meta-analysis of patients with IBD receiving infliximab to determine: the prevalence of ATI, the effect of antibodies to infliximab (ATI) on the prevalence of infusion reactions, and the effect of ATI on disease remission rates. Databases were searched through October 2011, and 18 studies involving 326 patients were included. Studies included 9 RCTs, 5 cohort studies, and 4 retrospective cohort studies. The prevalence of ATI was 45.8% when episodic infusions of infliximab were given and 12.4% when maintenance infliximab was given. The rates of infusion reactions were significantly higher in patients with ATI (relative risk [RR], 2.07; 95% confidence interval [CI], 1.61 to 2.67). Immunosuppressants resulted in a 50% reduction in the risk of developing ATI ($p < 0.001$). Patients with ATI were less likely to be in clinical remission, but this was not statistically significant (RR=0.90; 95% CI, 0.79 to 1.02; $p = 0.10$). The meta-analysis concluded that patients who test positive for ATIs are at an increased risk of infusion reactions, but have similar rates of remission compared with patients who test negative for ATIs.

Garces et al (2012) conducted a meta-analysis of studies of infliximab and adalimumab used to treat RA, ankylosing spondylitis, spondyloarthritis, psoriasis, CD, and UC. Databases were searched to August 2012, and 12 prospective cohort studies involving 860 patients (540 with RA, 132 with spondyloarthritis, 130 with IBD, 58 with psoriasis) were included. The outcome of interest was drug response, assessed by using standard assessment scales for rheumatologic diseases (eg, European League Against Rheumatism criteria for RA; Assessment in Ankylosing Spondylitis 20% response criteria, or ASDAS for spondyloarthritis; Psoriasis Area and Severity Index for psoriasis) and clinician assessment for IBD. Overall, detectable antidrug antibodies were associated with a 68% reduction in drug response (pooled RR=0.32; 95% CI, 0.22 to 0.48). Significant heterogeneity was introduced by varying use of immunosuppressant cotherapy (eg, methotrexate) across studies. To assess antidrug antibodies, most studies used RIA, which is less susceptible than ELISA to drug interference and may be more accurate.

Wang et al (2013) developed and validated a nonradiolabeled HMSA to measure antibodies-to-adalimumab (ATA) and adalimumab levels in serum samples. Analytic validation of performance characteristics (calibration standards, assay limits, intra- and interassay precision, linearity of dilution, substance interference) was performed for both the ATA- and adalimumab-HMSA. Because the elimination half-life of adalimumab (10-20 days) overlaps the dosing interval (every 2 weeks), ATA-positive sera to provide calibration standards were difficult to collect from human patients. (The drug-free interval for antibody formation is small.) Therefore, antisera from rabbits immunized with adalimumab were pooled to form calibration standards. Serial dilutions of these ATA calibration standards then generated a standard curve against which test samples were compared. Over 29 experimental runs, intra-assay precision and accuracy for the adalimumab-HMSA (as indicated by the CV) was $< 20\%$ and $< 3\%$, respectively; interassay (run-to-run, analyst-to-analyst, and instrument-to-instrument) precision and accuracy were less than 12% and less than 22%, respectively. For the ATA-HMSA, CVs for intra-assay precision and accuracy were less than 3% and less than 13%, respectively; CVs for interassay precision and accuracy were less than 9% and less than 18%, respectively. ELISA could not be used as a standard comparator due to competition from circulating drug. Analysis of 100 serum samples from patients who were losing response to adalimumab showed that 44% were above the cut point for ATA (0.55 U/mL), and 26% were below the cut point for serum adalimumab level. In samples below the adalimumab cut point (0.68 $\mu\text{g/mL}$), 68% were ATA positive; in samples with adalimumab levels greater than 20 $\mu\text{g/mL}$, 18% were ATA-positive.

In 2014, Steenholdt et al published a post hoc comparison of different ATI assays. Blood samples were collected from 66 (96%) of 69 patients enrolled in a randomized controlled trial (RCT) (discussed next) that assessed algorithmic treatment for Crohn disease (CD) relapse during infliximab therapy.⁵ Samples were analyzed by 3 binding assays; radioimmunoassay (RIA), ELISA, and HMSA, and by a reporter gene assay, a functional cell-based technique. ATI were detected in 18 patients (27%) by radioimmunoassay, 6 patients (9%) by ELISA, and 22 patients (33%) by HMSA. The reporter gene assay reported anti-infliximab activity, most likely due to ATI, in 7 patients (11%). As observed by the authors, this suggests that ATI detected by RIA and HMSA are not necessarily functionally active. Five patients (8%)

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were ATI-positive and 43 patients (65%) were ATI-negative by all 4 assays. Correlations were statistically significant ($p < 0.001$) in all pairwise comparisons (Pearson r , 0.77-0.96). However, statistical agreement between assays could not be estimated accurately (eg, using the intraclass correlation coefficient) because different assays reported values on different arbitrary scales. Regardless of assay used, most patients (74%-88%) had therapeutic serum infliximab levels and undetectable ATI, suggesting nonpharmacologic reasons for relapse or for symptoms mimicking relapse.

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. 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.

The clinical utility of vedolizumab (VDZ) trough levels (VTLs) in inflammatory bowel disease (IBD) is not well defined. The data to support the routine use of therapeutic drug monitoring during maintenance therapy is lacking. Further studies to determine the role of therapeutic drug monitoring of vedolizumab are needed.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*

CPT Codes

Code	Description
84999	Unlisted chemistry procedure

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HCPCS Codes

Code	Description
No code(s)	

ICD10 Codes

Code	Description
K50.00-K50.919	Crohn's disease [regional enteritis] (code range)
K51.00-K51.919	Ulcerative colitis (code range)
L40.50-L40.59	Arthropathic psoriasis (code range)
M05.40 – M05.471	Rheumatoid myopathy with rheumatoid arthritis (code range)
M06.4	Inflammatory polyarthropathy
M08.00-M08.09	Polyarticular juvenile rheumatoid arthritis, chronic or unspecified
M08.3	Juvenile rheumatoid polyarthrititis (seronegative)
M08.40-M08.48	Pauciarticular juvenile rheumatoid arthritis
M12.00-M12.09	Chronic postrheumatic arthropathy [Jaccoud]
M45.0-M45.9	Ankylosing spondylitis (code range)

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*Key Article

KEY WORDS

Antibodies to infliximab, antibodies to adalimumab, AnserTMIFX, AnserTMADA.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently no National Coverage Determination (NCD) or Local Coverage Determination (LCD) for Measurement of Serum Antibodies to Infliximab and Adalimumab.