# MEDICAL POLICY

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| MEDICAL POLICY DETAILS | |
|---|---|
| **Title** | **Measurement of Serum Antibodies to Tumor Necrosis Factor Blockers** |
| **Policy Number** | **2.02.47** |
| **Category** | **Technology Assessment** |
| **Original Effective Date** | **12/17/15** |
| **Committee Approval Date** | **12/15/16, 12/21/17** |
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| **Product Disclaimer** | • *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.*<br>• *If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.*<br>• *If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.*<br>• *If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) 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.*<br>• *If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.* |

## POLICY STATEMENT

I. Based upon our criteria and assessment of the peer-reviewed literature, measurement of antibodies to anti-tumor necrosis factor-α (anti-TNF-α) therapies, in patients receiving treatment, either alone or as a combination test that includes the measurement of serum to any of the following anti-TNF-α therapies are considered **investigational**:
   A. Infliximab
   B. Adalimumab
   C. Vedolizumab
   D. Ustekinumab

II. Measurement of antidrug antibodies in a patient receiving treatment with a biologic agent, either alone or as a combination test, which includes the measurement of serum TNF blocking agent levels, is considered **investigational**.

*Refer to Corporate Medical Policy #11.01.03 Experimental and Investigational Services*

## POLICY GUIDELINES

I. Infliximab, adalimumab, vedolizumab, and ustekinumab has received approval by the U.S. Food and Drug Administration (FDA).

II. Prometheus Laboratories Inc. offers non-radiolabeled, fluid-phase homogenous mobility shift assay (HMSA) tests called Anser IFX for infliximab, Anser ADA for adalimumab, Anser VDZ for vedolizumab, and Anser UST for ustekinumab. The four tests are not enzyme-linked immunosorbent assay (ELISA)-based; however, each can measure anti-drug antibodies in the presence of detectable drug levels, improving on a major limitation of the ELISA method. The tests measure serum drug concentrations and anti-drug antibodies.

III. The PrismRA (Scipher Medicine laboratory) test predicts the likelihood of non-response to TNFi therapies. The test analyzes 23 biological features, including RNA expression data, demographic variables, and disease-associated

clinical metrics, that are discriminatory between the molecular signatures of those who respond or do not respond adequately to TNFi therapies.

IV. These tests were developed, and the labs determined their performance characteristics. None has been cleared or approved by the United States Food and Drug Administration (FDA).

## DESCRIPTION

Infliximab (IFX), adalimumab (ADA), vedolizumab (VDZ), and ustekinumab (UST) are anti-tumor necrosis factor-α (anti-TNF-α) therapies. These therapies are effective when there is insufficient control of disease with conventional treatment in patients with inflammatory disorders, such bowel disease (IBD), ulcerative colitis, Crohn's disease, rheumatoid arthritis (RA), psoriatic arthritis, and ankylosing spondylitis. However, up to 30% of patients do not respond to anti-TNF-α therapy, and up to 60% of those who do respond to the therapy lose response over time. Options for those who do not respond include increasing the dose interval, increasing the dose, or changing to another anti-TNF drug or to a drug from a different class. It is unclear why some patients have no response or lose response. The reason for nonresponse or loss of response is unclear, but it may be due to formation of antibodies to anti-TNF agents. Antibodies to IFX, or ATI, also referred to as human antichimeric antibodies (HACAs), are reported to develop in up to approximately 60% of patients depending on the dosing schedule, the 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 that results in decreased efficacy. Antidrug antibodies have also been associated with acute infusion reactions and delayed hypersensitivity reactions. Adalimumab is considered less immunogenic than 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 antidrug antibodies can be accomplished by 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 anti-drug 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 ATI, (referred to as 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's 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 were identified in 51 patients (33%). Of 177 tests assessed, the results impacted treatment decisions in 73% of patients. 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 suitable alternative to changing to another anti-TNF agent. Limitations to the study included its retrospective design and the use of the ELISA method to test for antibodies to infliximab. 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 ATI and residual circulating infliximab levels prior to another infusion were associated with acquired infliximab resistance in RA. A multi-variate 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), while the presence of ATI 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 ATI 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 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. The studies included nine randomized, controlled trials (RCTs), five cohort studies, and four 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 ATI are at an increased risk of infusion reactions but have similar rates of remission compared with patients who test negative for ATI.

Garces et al. (2012) conducted a meta-analysis of studies of infliximab and adalimumab used to treat RA, ankylosing spondylitis, spondyloarthritis, psoriasis, Crohn's disease (CD), and ulcerative colitis (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 (e.g., 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 (e.g., 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 non-radiolabeled HMSA to measure antibodies-to-adalimumab (ATA) and adalimumab levels in serum samples. Analytic validation of performance characteristics (calibration standards, assay limits, intra- and inter-assay 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 two 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, anti-sera 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 the course of 29 experimental runs, intra-assay precision and accuracy for the adalimumab-HMSA (as indicated by the CV) was <20% and <3%, respectively; inter-assay (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 inter-assay 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 the 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 μg/mL), 68% were ATA-positive; in samples with adalimumab levels greater than 20 μg/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 of 69 patients enrolled in an RCT (discussed next) that assessed algorithmic treatment for CD relapse during infliximab therapy. Samples were analyzed by three binding assays: RIA, ELISA, and HMSA; and by a reporter gene assay, a functional cell-based technique. ATI were detected in 18 patients (27%) by radioimmunoassay, six patients (9%) by ELISA, and 22 patients (33%) by HMSA. The reporter gene assay reported anti-infliximab activity, most likely due to ATI, in seven patients (11%). As observed by the authors, this suggests that ATI detected by RIA and HMSA are not necessarily functionally active. Five patients (8%) were ATI-positive and 43 patients (65%) were ATI-negative by all four 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 (e.g., 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.

ATI or 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 trough levels (VTLs) in IBD is not well-defined. The data to support the routine use of therapeutic drug-monitoring during maintenance therapy are 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.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

**CPT Codes**

| Code | Description |
|---|---|
| 80145 **(E/I)** | Adalimumab (Therapeutic level testing) |
| 80230 **(E/I)** | Infliximab (Therapeutic level testing) |
| 80280 **(E/I)** | Vedolizumab (Therapeutic level testing) |
| 84999 | Unlisted chemistry procedure |
| 0456U **(E/I)** | Autoimmune (rheumatoid arthritis), next-generation sequencing (NGS), gene expression testing of 19 genes, whole blood, with analysis of anti-cyclic citrullinated peptides (CCP) levels, combined with sex, patient global assessment, and body mass index (BMI), algorithm reported as a score that predicts nonresponse to tumor necrosis factor inhibitor (TNFi) therapy *(Effective 07/01/24)* |

**HCPCS Codes**

| Code | Description |
|---|---|
| J0135 | Injection, adalimumab, 20 mg |
| J1745 | Injection, infliximab, excludes biosimilar, 10 mg |
| J3357 | Ustekinumab, for subcutaneous injection, 1 mg |
| J3358 | Ustekinumab, for intravenous injection, 1 mg |
| J3380 | Injection, vedolizumab, 1 mg |

**ICD10 Codes**

| Code | Description |
|---|---|
| K50.00-K50.919 | Crohn's disease (code range) |
| K51.00-K51.919 | Ulcerative (chronic) pancolitis (code range) |
| L40.50-L40.59 | Arthropathic psoriasis (code range) |
| M05.40 – M05.479 | Rheumatoid myopathy with rheumatoid arthritis (code range) |
| M06.4 | Inflammatory polyarthropathy |
| M08.00-M08.09 | Juvenile rheumatoid arthritis (code range) |
| M08.3 | Juvenile rheumatoid polyarthritis (seronegative) |
| M08.40-M08.48 | Pauciarticular juvenile rheumatoid arthritis (code range) |
| M12.00-M12.09 | Chronic postrheumatic arthropathy [Jaccoud] (code range) |
| M45.0-M45.9 | Ankylosing spondylitis of the spine (code range) |

## REFERENCES

*Afif W, et al. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. Am J Gastroenterol 2010 May;105(5):1133-39.

*Bartelds GM, et al. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. JAMA 2011 Apr 13;(305(14):1460-8.

Benucci M, et al. Antidrug antibodies against TNF-blocking agents; correlations between disease activity, hypersensitivity reactions, and different classes of immunoglobulins. Biologics 2015 Feb 17;9:7-12.

Bodini G, et al. Adalimumab trough serum levels and anti-adalimumab antibodies in the long-term clinical outcomes of patients with Crohn’s disease. Scand J Gastroenterol 2016 Sept;51(9):1081-6.

Cludt I, et al. Anti-therapeutic antibodies and their clinical impact in patients treated with the TNF antagonist adalimumab. Cytokine Aug 2017;96:16-23.

*Finckh A, et al. Influence of anti-infliximab antibodies and residual infliximab concentrations on the occurrence of acquired drug resistance to infliximab in rheumatoid arthritis patients. Joint Bone Spine 2010 Jul;77(4):313-8.

Frederiksen MT, et al. Antibodies against infliximab are associated with de novo development of antibodies to adalimumab and therapeutic failure in infliximab-to adalimumab switchers with IBD. Inflamm Bowel Dis 2014 Oct;20(10):1714-21.

*Garces S, et al. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory disease: a systematic review of the literature with a meta-analysis. Ann Rheum Dis 2013;72(12)1947-55.

*Lee LY, et al. Anti-Infliximab antibodies in inflammatory bowel disease: prevalence, infusion reactions, immunosuppression and response, a meta-analysis. Eur J Gastroenterol Hepatol 2012 May 27;24(9):1078-85.

Nanda KS, et al. Impact of antibodies to infliximab on clinical outcomes and serum infliximab levels in patients with inflammatory bowel disease (IBD): a meta-analysis. Am J Gastroenterol 2013 Jan;108(1):40-47.

Nencini F, et al. The kinetics and antidrug antibodies, drug levels, and clinical outcomes in infliximab-exposed patients with immune-mediated disorders. J Allergy Clin Immunol Pract 2018 Nov-Dec;6(6):2065-2072.

Meroni PL, et al. New strategies to address the pharmacodynamics and pharmacokinetics of tumor necrosis factor (TNF) inhibitors: a systematic analysis. Autoimmun Rev 2015 Sep;14(9):812-29.

Mould DR, et al. Dashboard systems: pharmacokinetic/pharmacodynamic mediated dose optimization for monoclonal antibodies. J Clin Pharmacol 2015 Mar;55(Suppl 3):S51-9.

Pecoraro V, et al. The impact of immunogenicity of TNFα inhibitors in autoimmune inflammatory disease. A systematic review and meta-analysis. Autoimmun Rev 2017 Jun;16(6):564-575.

*Steenholdt C, 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 2014 Jul;109(7):1055-64.

*Steenholdt C, et al. Individualized therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomized, controlled trial. Gut 2014 Jun;63(6):919-27.

Stein R, et al. Serum infliximab, antidrug antibodies, and tumor necrosis factor predict sustained response in pediatric Crohn's disease. Inflamm Bowel Dis 2016 Jun;2296):1370-7.

Vande Casteele N, et al. Pharmacokinetics of anti-TNF monoclonal antibodies in inflammatory bowel disease: adding value to current practice. J Clin Pharmacol 2015 Mar;55(Suppl3):S39-50.

Vande Casteele N, et al. The relationship between infliximab concentrations, antibodies to infliximab and disease activity in Crohn's disease. Gut 2015 Oct;64(10):1539-45.

*Wang SL, et al. Monitoring of adalimumab and antibodies-to-adalimumab levels in patient serum by the homogeneous mobility shift assay. J Pharm Biomed Anal 2013 May 5;78-79:39-44.

*Key Article

## KEY WORDS

Antibodies to infliximab, antibodies to adalimumab, AnserIFX, AnserADA, Anser VDZ, Anser UST.

## 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.