Medical Coverage Policy | Measurement of Serum Antibodies to Selected Biologic Agents

EFFECTIVE DATE: 01|01|2020
POLICY LAST UPDATED: 2|02|2022

OVERVIEW

Biologic agents used to treat autoimmune diseases include infliximab, adalimumab, vedolizumab, and ustekinumab. Infliximab (Remicade) is an intravenous tumor necrosis factor α 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) is a subcutaneous tumor necrosis factor α inhibitor that is FDA approved for the treatment of Crohn's disease and ulcerative colitis in adults and those with juvenile idiopathic arthritis. Vedolizumab (Entyvio) is an intravenous integrin receptor antagonist that is FDA approved for treatment of ulcerative colitis and Crohn's Disease in adults. Ustekinumab (Stelara) is an intravenous and subcutaneous human interleukin-12 and -23 antagonist that is FDA approved for the treatment of psoriatic psoriasis, Crohn's disease, and ulcerative colitis in adults, and plaque psoriasis in adolescents and adults. Following the primary response to these medications, some patients become secondary nonresponders. The development of antidrug antibodies is considered a cause of this secondary nonresponse.

Currently, selected U.S. Food and Drug Administration approved biologic agents include infliximab, adalimumab, vedolizumab, and ustekinumab.

MEDICAL CRITERIA

Not applicable

PRIOR AUTHORIZATION

Not applicable

POLICY STATEMENT

Medicare Advantage Plans

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 not covered as the evidence is insufficient to determine the effects of the technology on health outcomes.

Commercial Products

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 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 Evidence of Coverage for applicable not medically necessary/not covered benefits/coverage.

BACKGROUND

Infliximab, Adalimumab, Vedolizumab, and Ustekinumab in Autoimmune Diseases

Biologic agents (e.g. infliximab, adalimumab, vedolizumab, or ustekinumab) are used to treat multiple inflammatory conditions, including rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, inflammatory bowel disease (eg, Crohn disease, ulcerative colitis), ankylosing spondylitis, and plaque

psoriasis. These agents are generally given to patients who fail conventional medical therapy, and they are typically highly effective for the induction and maintenance of clinical remission. However, not all patients respond, and a high proportion of patients lose response over time. It is estimated that 1 in 3 patients do not respond to induction therapy (primary nonresponse); further, among initial responders, response wanes over time in approximately 20% to 60% of patients (secondary nonresponse). The reasons for therapeutic failures remain a matter of debate but include accelerated drug clearance (pharmacokinetics) and neutralizing agent activity (pharmacodynamics) due to antidrug antibodies (ADA). ADA is also associated with injection-site reactions and acute infusion reactions and delayed hypersensitivity reactions.

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 (ie, enzyme-linked immunosorbent assays [ELISA]) can measure only ADA in the absence of detectable drug levels, due to the interference of the drug with the assay. Other techniques available for measuring antibodies include the radioimmunoassay method and, more recently, the homogenous mobility shift assay using high-performance liquid chromatography. Disadvantages of the radioimmunoassay method are associated with the complexity of the test and prolonged incubation time, along with safety concerns related to the handling of radioactive material. The homogenous mobility shift assay measures ADA when infliximab is present in serum. Studies evaluating the validation of results among different assays are lacking, making interstudy comparisons difficult. One retrospective study by Kopylov et al (2012), which evaluated 63 patients, demonstrated comparable diagnostic accuracy between 2 different ELISA methods in patients with inflammatory bowel disease(ie, double-antigen ELISA and antihuman lambda chain-based ELISA).This study did not include an objective clinical and endoscopic scoring system for validation of results.

Treatment Options for Secondary Nonresponse to Biologic Agents

A diminished or suboptimal response to infliximab, adalimumab, vedolizumab, or ustekinumab can be managed in several ways: shortening the interval between doses, increasing the dose, switching to a different biologic agent (in patients who continue to have a loss of response after receiving the increased dose), or switching to a non-biologic agent.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Prometheus Laboratories, a College of American Pathologists-accredited lab under the Clinical Laboratory Improvement Amendments, offers four non-radio-labeled, fluid-phase homogenous mobility shift assay tests: called Anser IFX (for infliximab), Anser ADA (for adalimumab), Anser VDZ (for vedolizumab), and Anser UST (for ustekinumab). The tests measure both serum drug concentrations and ADA. They are not based on an ELISA test, and can measure ADA in the presence of detectable drug levels, improving on a major limitation of the ELISA method.

For individuals who have rheumatoid arthritis, psoriatic arthritis, or juvenile idiopathic arthritis; inflammatory bowel disease (eg, Crohn disease, ulcerative colitis); ankylosing spondylitis; or plaque psoriasis who receive evaluation for serum antibodies to infliximab, adalimumab, vedolizumab, or ustekinumab, the evidence includes multiple systematic reviews, a randomized controlled trial, and observational studies. Relevant outcomes are test validity, change in disease status, health status measures, quality of life, and treatment-related morbidity. Antibodies to biologic agents 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 and secondary nonresponse as well as injection-site and infusion-site

reactions. The clinical usefulness of measuring antidrug antibodies 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 antidrug antibodies. A small randomized controlled trial in patients with Crohn's disease comparing antidrug -informed management of relapse with standard dose escalation did not demonstrate improved outcomes with the antidrug antibody -informed approach. Additionally, many assays, some having significant limitations, have been used in studies; antidrug antibody 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.

CODING

The following CPT code(s) are considered not covered for Medicare Advantage Plans and not medically necessary for Commercial products:

80145 Adalimumab
80230 Infliximab
80280 Vedolizumab

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

84999 Unlisted chemistry procedure

RELATED POLICIES

None

PUBLISHED

Provider Update, April 2022
Provider Update, March 2021
Provider Update, March 2020
Provider Update, November 2019
Provider Update, Nov. /Dec. 2018

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. Inflamm Bowel Dis. Sep 2012; 18(9): 1628-33. PMID 22038899
3. 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: Agency for Healthcare Research and Quality; 2009. https://www.ncbi.nlm.nih.gov/books/NBK47094/. Accessed October 5, 2021.
4. 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
5. 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. Ann Rheum Dis. Dec 2013; 72(12): 1947-55. PMID 23223420
6. 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. Sep 2012; 24(9): 1078-85. PMID 22647738

7. 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. Am J Gastroenterol. Jan 2013; 108(1): 40-7; quiz 48. PMID 23147525
8. Thomas SS, Borazan N, Barroso N, et al. Comparative Immunogenicity of TNF Inhibitors: Impact on Clinical Efficacy and Tolerability in the Management of Autoimmune Diseases. A Systematic Review and Meta-Analysis. BioDrugs. Aug 2015; 29(4): 241-58. PMID 26280210
9. Pecoraro V, De Santis E, Melegari A, et al. The impact of immunogenicity of TNF inhibitors in autoimmune inflammatory disease. A systematic review and meta-analysis. Autoimmun Rev. Jun 2017; 16(6): 564-575. PMID 28411169
10. Cludts I, Spinelli FR, Morello F, et al. Anti-therapeutic antibodies and their clinical impact in patients treated with the TNF antagonist adalimumab. Cytokine. Aug 2017; 96: 16-23. PMID 28279855
11. Ara-Martin M, Pinto PH, Pascual-Salcedo D. Impact of immunogenicity on response to anti-TNF therapy in moderate-to-severe plaque psoriasis: results of the PREDIR study. J Dermatolog Treat. Nov 2017; 28(7): 606-612. PMID 28274164
12. Lombardi G, Perego S, Sansoni V, et al. Anti-adalimumab antibodies in psoriasis: lack of clinical utility and laboratory evidence. BMJ Open. Dec 09 2016; 6(12): e011941. PMID 27940624
13. Arstikyte I, Kapleryte G, Butrimiene I, et al. Influence of Immunogenicity on the Efficacy of Long-Term Treatment with TNF Blockers in Rheumatoid Arthritis and Spondyloarthritis Patients. Biomed Res Int. 2015; 2015: 604872. PMID 26064930
14. van Gestel AM, Prevoo ML, van 't Hof MA, et al. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. Arthritis Rheum. Jan 1996; 39(1): 34-40. PMID 8546736
15. Castillo-Gallego C, Aydin SZ, Marzo-Ortega H. Clinical utility of the new ASAS criteria for spondyloarthritis and the disease activity score. Curr Rheumatol Rep. Oct 2011; 13(5): 395-401. PMID 21748416
16. Jani M, Chinoy H, Warren RB, et al. Clinical utility of random anti-tumor necrosis factor drug-level testing and measurement of antidrug antibodies on the long-term treatment response in rheumatoid arthritis. Arthritis Rheumatol. May 2015; 67(8): 2011-9. PMID 26109489
17. Frederiksen MT, Ainsworth MA, Brynskov J, 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. Oct 2014; 20(10): 1714-21. PMID 25069030
18. Vande Casteele N, Gils A, Singh S, et al. Antibody response to infliximab and its impact on pharmacokinetics can be transient. Am J Gastroenterol. Jun 2013; 108(6): 962-71. PMID 23419382
19. Eser A, Primas C, Reinisch W. Drug monitoring of biologics in inflammatory bowel disease. Curr Opin Gastroenterol. Jul 2013; 29(4): 391-6. PMID 23703367
20. Khanna R, Sattin BD, Afif W, et al. Review article: a clinician's guide for therapeutic drug monitoring of infliximab in inflammatory bowel disease. Aliment Pharmacol Ther. Sep 2013; 38(5): 447-59. PMID 23848220
21. Lichtenstein GR. Comprehensive review: antitumor necrosis factor agents in inflammatory bowel disease and factors implicated in treatment response. Therap Adv Gastroenterol. Jul 2013; 6(4): 269-93. PMID 23814608
22. Garces S, Antunes M, Benito-Garcia E, et al. A preliminary algorithm introducing immunogenicity assessment in the management of patients with RA receiving tumour necrosis factor inhibitor therapies. Ann Rheum Dis. Jun 2014; 73(6): 1138-43. PMID 23666932
23. Syversen SW, Goll GL, Jorgensen KK, et al. Effect of Therapeutic Drug Monitoring vs Standard Therapy During Infliximab Induction on Disease Remission in Patients With Chronic Immune-Mediated Inflammatory Diseases: A Randomized Clinical Trial. JAMA. May 04 2021; 325(17): 1744-1754. PMID 33944876
24. 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): 919-27. PMID 23878167

25. Steenholdt C, Bendtzen K, Brynskov J, et al. Cut-off levels and diagnostic accuracy of infliximab trough levels and anti-infliximab antibodies in Crohn's disease. Scand J Gastroenterol. Mar 2011; 46(3): 310-8. PMID 21087119
26. Tan M. Importance of defining loss of response before therapeutic drug monitoring. Gut. Mar 2015; 64(3): 516-7. PMID 25031226
27. Roblin X, Rinaudo M, Del Tedesco E, et al. Development of an algorithm incorporating pharmacokinetics of adalimumab in inflammatory bowel diseases. Am J Gastroenterol. Aug 2014; 109(8): 1250-6. PMID 24913041
28. Roblin X, Marotte H, Rinaudo M, et al. Association between pharmacokinetics of adalimumab and mucosal healing in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. Jan 2014; 12(1): 80-84.e2. PMID 23891927
29. Afif W, Loftus EV, Faubion WA, et al. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. Am J Gastroenterol. May 2010; 105(5): 1133-9. PMID 20145610
30. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol. Mar 2019; 114(3): 384-413. PMID 30840605
31. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. Apr 2018; 113(4): 481-517. PMID 29610508
32. Feuerstein JD, Nguyen GC, Kupfer SS, et al. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. Gastroenterology. Sep 2017; 153(3): 827-834. PMID 28780013
33. 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]. 2016; https://www.nice.org.uk/guidance/dg22/chapter/1-Recommendations. Accessed October 5, 2021.
34. National Institute for Health and Care Excellence (NICE). Therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis [DG36]. 2019; https://www.nice.org.uk/guidance/dg36/chapter/1-Recommendations. Accessed October 4, 2021