AmeriHealth Caritas Ohio

Measurement of serum antibodies to Infliximab and Adalimumab

Clinical Policy ID: CCP.1194

Recent review date: 12/2025

Next review date: 4/2027

Policy contains: Adalimumab; anti-drug antibody; immunoassay; immunogenicity; infliximab.

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Coverage policy

Measurement of serum anti-drug antibodies to infliximab and adalimumab is clinically proven and, therefore, may be medically necessary for members with active Crohn's disease who meet all of the following criteria (American College of Gastroenterology [Lichtenstein, 2025]; American Gastroenterological Association Institute [Feuerstein, 2017]):

- Member has documented infliximab or adalimumab drug treatment failure.
- Drug trough levels are subtherapeutic.
- The information will impact clinical management.

For any determinations of medical necessity for medications, refer to the applicable state approved pharmacy policy.

Limitations

All other uses of anti-drug antibody measurement to infliximab and adalimumab are experimental/investigational and not clinically proven including, but not limited to, during induction treatment or proactively irrespective of disease activity status (Feuerstein, 2017; Lichtenstein, 2025).

Alternative covered services

- Serum drug level monitoring.

- Guideline-directed care for chronic inflammatory disorders.

Background

Tumor necrosis factor-α inhibitors can be effective treatment options for patients with inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, along with immune disorders such as psoriasis and various forms of arthritis. Infliximab and adalimumab are the most common tumor necrosis factor-α inhibitors. Biosimilars are emerging that expand treatment options for chronic inflammatory conditions and other clinical applications.

However, approximately one-third of patients with immune-mediated inflammatory diseases treated with anti-tumor necrosis factor-α biologic therapies do not respond, and more experience a waning response after initial success. The precise mechanism of a subtherapeutic response has not been fully explained. As monoclonal antibodies, anti-tumor necrosis factor-α inhibitors can elicit an immune response, producing anti-drug antibodies that are associated with reduced or undetectable drug levels, loss of drug efficacy, clinical non-response, and an increased risk of adverse effects (Ogric, 2017). Rates of anti-drug antibodies to infliximab and adalimumab monotherapy are estimated to be 28.0% and 7.5%, respectively, in patients with inflammatory bowel disease (Bots, 2021).

Therapeutic drug monitoring of serum drug levels and anti-drug antibodies has been proposed as means of improving disease management, patient outcomes, and quality of life. Therapeutic drug monitoring may be proactive or reactive. Proactive therapeutic drug monitoring involves measuring serum drug levels and anti-drug antibodies irrespective of disease activity, followed by adjusting drug dosing to achieve pre-specified target serum drug levels. Reactive therapeutic drug monitoring measures drug concentrations and anti-drug antibodies when triggered by a clinical event (Kawano-Dourado, 2024).

Most current anti-drug antibody assays are drug-sensitive and cannot be used close to drug administration when the drug concentration is too high, which may produce false-negative results. To overcome these limitations, new testing methods have been developed that enable anti-drug antibody measurement in the presence of the drug, i.e., drug-tolerant assays. These assays may allow for proactive, early detection of anti-drug antibodies, before a patient experiences clinical symptoms or a loss of response, which, in turn, may predict immunogenicity and drug survival (Martinez-Feito, 2025). This would allow the practitioner to discern the effects of these medications and, potentially, biosimilars, in patients who showed improvement and in those whose benefits have waned over time in a substantial proportion of cases.

Findings

This policy focuses on the clinical benefits of therapeutic drug monitoring using drug-sensitive and drug-tolerant anti-drug antibody assays for patients on infliximab or adalimumab. The following guidelines recommend reactive therapeutic drug monitoring as the standard of care for persons who are failing anti-tumor necrosis factor drug treatment, and only testing for the presence of anti-drug antibodies when drug trough levels are low, to aid in understanding the reasons for treatment failure and developing subsequent treatment schedule. There is no consensus on which type of assay to recommend.

The guidelines recommend against therapeutic drug monitoring of anti-drug antibodies as a means of optimizing therapy during induction and preventing future flare-ups and loss of response, or proactively during maintenance treatment. The long-term effects of any changes in clinical management are unknown, and the cost effectiveness is unclear. The main barrier to anti-drug antibody testing in daily clinical practice is the lack of a universally valid assay and the absence of a cutoff level clearly correlated with a clinical outcome.

Guidelines

The American College of Gastroenterology recommends considering therapeutic drug monitoring to assess anti-tumor necrosis factor drug levels and anti-drug antibody status for individuals with documented active Crohn's disease receiving anti-tumor necrosis factor therapies, particularly among those who develop secondary loss of response. In this setting, the results could be used to explain the cause of biologic failure (i.e., to differentiate among mechanistic failure, immune-mediated drug failure, and non–immune-mediated drug failure) and guide subsequent treatment decisions. There is insufficient evidence of a clinical benefit to recommend proactive therapeutic drug monitoring for patients on anti- tumor necrosis factor treatment for Crohn's disease (Lichtenstein. 2025).

The American Gastroenterological Association Institute guideline (Feuerstein, 2017) conditionally recommends reactive therapeutic drug monitoring in adults with active inflammatory bowel disease treated with anti-tumor necrosis factor agents, to guide treatment changes, based on a technical review finding very low-quality supportive evidence, primarily in individuals with Crohn's disease. For adults with quiescent inflammatory bowel disease treated with anti-tumor necrosis factor agents, the Association issued no recommendation regarding the use of routine proactive therapeutic drug monitoring, as the overall benefits and potential harms of this strategy remain uncertain (Vande Casteele, 2017).

North American guidelines for rheumatoid arthritis (Fraenkel, 2021) and psoriasis (Menter, 2019) do not address anti-drug antibody testing in the management of these diseases.

Evidence review

The majority of studies evaluating the clinical utility of therapeutic drug monitoring in chronic inflammatory disorders have used only drug-sensitive assays. This limits the ability to assess immunogenicity to when the drug is not measurable in serum. Studies of drug-tolerant assays have emerged that may expand the clinical utility of therapeutic drug monitoring to a proactive role during induction or maintenance treatment, but the clinical benefit is unclear.

The quality of the evidence is low, and results from randomized controlled trials are sparse. The strongest evidence from the following systematic reviews and meta-analyses exists for adults on infliximab treatment for inflammatory bowel disorders, and Crohn's disease, in particular. For patients treated with adalimumab and for children, the evidence was limited in quality and quantity. Studies varied with respect to the type of test used, response criteria, and populations enrolled (Barrau, 2023; Silva-Ferreira, 2016).

Recent systematic reviews and meta-analyses of proactive therapeutic drug monitoring have produced similar findings. In studies of individuals with immune-mediated inflammatory diseases, the majority included adults with inflammatory bowel disease and, to a lesser extent, inflammatory arthritis and psoriasis treated with infliximab. The evidence is insufficient to support the effectiveness of proactive therapeutic drug monitoring of infliximab or adalimumab during induction, or adalimumab during maintenance. Proactive therapeutic drug monitoring with infliximab during maintenance may increase the proportion of patients who experienced sustained disease control or remission, may reduce disease worsening, but may have little or no effect on quality of life, physical function, or mental health. The effects of proactive therapeutic drug monitoring appeared to be consistent across the different immune-mediated diseases. Follow up periods did not exceed one year, making the long term effects of proactive therapeutic drug monitoring uncertain (Zeraatkar, 2024; 10 randomized controlled trials).

In participants with active and quiescent inflammatory bowel disease who received infliximab or adalimumab, proactive therapeutic drug monitoring was not superior to standardized therapy or conventional management for maintaining clinical remission (relative risk 1.16, 95% confidence interval 0.98 to 1.37, n = 528). Limited observational data suggest it may increase the treatment durability and safety, avoid acute infusion reactions and the appearance of anti-drug antibodies, and reduce the probability of surgery, but long-term results are needed (Manceñido Marcos, 2024).

For patients with inflammatory bowel disease or rheumatoid arthritis receiving adalimumab, a meta-analysis of nine randomized and nonrandomized studies found proactive therapeutic drug monitoring was not superior to reactive therapeutic drug monitoring or conventional management in achieving or maintaining clinical remission (63.42% vs. 55.44%, relative risk 1.24, 95% confidence interval 0.98 to 1.58, four studies). For patients experiencing treatment failure, reactive therapeutic drug monitoring can aid in understanding the reasons for treatment failure and in developing subsequent treatment schedules (Li, 2024; five studies).

Cost effectiveness

A systematic review of six model-based, cost-effectiveness analyses found that therapeutic drug monitoring in people with Crohn's disease treated with infliximab may be cost saving and cost effective compared to standard of care. However, the effectiveness of interventions guided by therapeutic drug monitoring was highly dependent on the clinical management algorithms applied (such as proactive or reflexing testing) (Yao, 2021). In another systematic review, there was insufficient evidence on cost effectiveness to permit conclusions regarding therapeutic drug monitoring in individuals with rheumatoid arthritis (Tikhonova, 2021).

In 2016, we added four peer-reviewed references.

In 2017, we did not identify any newly published systematic reviews, meta-analyses, or guidelines.

In 2018, we updated the references. The policy ID changed from 01.01.03 to CCP.1194.

In 2019, we added one peer-reviewed publication to the reference list.

In 2020, we updated the references. No policy changes are warranted.

In 2021, we updated the references and added no new relevant literature to the policy. No policy changes are warranted.

In 2022, we updated the references and added no new relevant literature to the policy. No policy changes are warranted.

In 2023, we updated the references and added no new relevant literature to the policy. No policy changes are warranted.

In 2024, we found no policy changes were warranted.

In 2025, we updated the references, added several new evidence reviews and guidelines, and deleted older references. We modified coverage to align with guideline recommendations for anti-drug antibody monitoring in persons with inflammatory bowel disease treated with infliximab or adalimumab.

References

On October 8, 2025, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were "serum antibodies," "immunogenicity," "infliximab," and "adalimumab." We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

9/2015: initial review date and clinical policy effective date: 1/2016

12/2016: Policy references updated.

12/2017: Policy references updated.

12/2018: Policy references updated. Policy ID changed from 01.01.03 to CCP.1194.

12/2019: Policy references updated.

12/2020: Policy references updated.

12/2021: Policy references updated.

12/2022: Policy references updated.

12/2023: Policy references updated.

12/2024: Policy references updated.

12/2025: Policy references updated. Coverage modified.