Measurement of serum antibodies to Infliximab and Adalimumab

Clinical Policy ID: CCP.1194

Recent review date: 12/2024

Next review date: 4/2026

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

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Coverage policy

The measurement of serum antibodies to the drugs infliximab and adalimumab, taken either alone or in combination, is investigational/not clinically proven and, therefore, not medically necessary.

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

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

No alternative covered services were identified during the writing of this policy.

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 (Ogric, 2017). The precise mechanism of the lack of therapeutic 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.

In cases of suspected drug failure, and to better define clinical efficacy, serum drug levels and anti-drug antibody testing have been proposed as means of improving disease management, patient outcomes, and quality of life. Infliximab and adalimumab levels can be measured by many different assay detection methods, but enzyme-linked immunoassay and radioimmunoassay are most common (Ogric, 2017). Most current assays that measure anti-drug antibodies cannot detect antibodies complexed with the drug, resulting in 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. This would allow the practitioner to discern the effects of these medications and, potentially, biosimilars, on patients who showed improvement, and those whose benefits have been found to wane over time in a substantial proportion of cases.

Findings

Researchers have struggled to develop an effective and consistent means of measuring serum antibody level of antibodies to infliximab and to adalimumab. Early efforts could only measure antibodies when drug levels were absent and could not interfere with the assay. The radioimmunoassay approach was hampered by text complexity, long incubation periods, and radiation safety issues.

Perhaps the most crucial aspect of serum antibody testing for infliximab and adalimumab is the lack of demonstrated use to alter clinical practices of using infliximab or adalimumab according to results. Several trials concur that greater efforts are needed due to this lack of utility. The Yanai study on inflammatory bowel disease states, “Prospective controlled trials are direly needed to investigate the optimal tailored management in individual patients who lose response” (Yanai, 2011).

Antibodies to infliximab and adalimumab are assessed using a variety of techniques, and thus, results of measurements cannot be compared for clinical purposes (Valor, 2015). Lowest levels of detection also vary by assay and are not comparable (Steenholdt, 2013). A meta-analysis of 11 studies found detectable antibodies to infliximab in patients with irritable bowel syndrome ranging from 22% to 46%, but authors concluded that the true incidence of antibodies to infliximab after infliximab is unknown “due to the different administration schedules, timing of measurements of antibodies to infliximab, methods used in antibodies to infliximab detection, and the presence of serum infliximab” (Nanda, 2013).

Another meta-analysis showed that in 18 studies of 3,326 participants given infliximab, antibodies to the drug were prevalent in just 45.8% and 12.4% given episodic infusions and maintenance treatments, respectively. The authors conclude that patients who test positive for antibodies to infliximab have an elevated risk of infusion reactions, but the same risk of remission as do patients testing negative for antibodies to infliximab (Lee, 2012).

A meta-analysis and systematic review of 68 studies, mostly patients with rheumatoid arthritis or irritable bowel syndrome, found that the presence of an antidrug antibody was linked with reduced odds of response, and immunosuppressants decreased the risk of these antibodies. Presence of antibodies to infliximab varied by study, with a high of 25.3%. However, fewer than half of the studies were rated as good quality (Thomas, 2015). A 2015 systematic review also found varying levels of antibodies to infliximab presence by study, and a link

between presence of antibodies to infliximab and lower risk of disease control or remission; the authors note a lack of homogeneity in study design/methodology, along with varying results from different assays (Meroni, 2015).

Another systematic review on immunogenicity in Crohn's disease found "no clear evidence that anti-infliximab antibodies have an impact on efficacy or safety, nor a need to measure or prevent them in clinical practice" (Cassinotti, 2009).

In 2016, we added four peer-reviewed references.

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

In 2018, we added a technical review published by the American Gastroenterological Association Institute (Vande Casteele, 2017) and guidelines based on the technical review (Feuerstein, 2017). The guidelines conditionally recommend, based on very low-quality evidence, reactive therapeutic drug monitoring (to be administered when a patient's initial response later lags). A review article published by authors from Australia, New Zealand, the United States, and Canada, based on a study utilizing the Delphi technique and sponsored by the Gastroenterological Society of Australia, offered compatible guidelines (Mitrev, 2017).

The American College of Gastroenterology published a revised guideline (Lichtenstein, 2018) that states that in documented active Crohn's disease, "assessment of biologic drug levels and antidrug antibodies (therapeutic drug monitoring) should be considered." The above four publications have been added to the reference list. 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 added a diagnostic guideline from the National Institute for Health and Care Excellence (2019a) that does not recommend therapeutic monitoring of tumor necrosis factor-α inhibitors in rheumatoid arthritis due to insufficient evidence of clinical effectiveness, along with the Institute's guideline on Crohn's disease (2019b).

We added a systematic review (Gorovits, 2018) of clinical immunoassay methods used for detection of anti-drug antibodies to adalimumab and infliximab, which found that regardless of assay format or biological used, anti-drug antibody formation was associated with lower serum concentrations, reduced drug efficacy, and elevated rates of infusion-related reactions. The investigators called for greater consistency in reporting of assay methods and clinical consequences of anti-drug antibody formation, and in standardizing immunogenicity testing and reporting to improve knowledge of the impact of immunogenicity to biologics. The new results are consistent with previous findings and 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 added a systematic review/meta-analysis of 33 articles (n = 5,850) that placed rates of anti-drug antibodies for biologic monotherapy for infliximab and adalimumab to be 28.0% and 7.5%, respectively, in patients with inflammatory bowel disease (Bots, 2021).

In 2023, we added a systematic review of 90 studies assessing patients treated with anti-tumor necrosis factor therapies, often infliximab, for inflammatory bowel disease. Drug-tolerant assays against infliximab or adalimumab can predict primary non-response/loss of response. Drug-sensitive assays do not allow detection of anti-drug antibodies during induction, when concentration of infliximab or adalimumab are high (Barrau, 2023).

We also added a systematic review of 41 studies of 99 biomarkers in patients with rheumatoid arthritis. No biomarker consistently showed a strong predictive effect for response to tumor necrosis inhibitor factors, including infliximab and adalimumab, which authors termed "disappointing" (Wientjes, 2022).

In 2024, we found a relevant systematic review from 2016 of 20 studies (n = 2,800) focusing on the measurement of serum antibodies to infliximab and adalimumab in patients with inflammatory bowel disease. These studies encompassed both adults and children with Crohn's disease and ulcerative colitis. The review found that measuring drug and antidrug antibody levels was associated with significant clinical outcomes, such as clinical remission, loss of response, and mucosal healing. The authors emphasized that monitoring these levels during maintenance therapy—especially in cases of loss of response, persistent high levels of C-reactive protein, or ongoing mucosal lesions—can guide treatment adjustments and improve patient outcomes (Silva-Ferreira, 2016). No policy changes were warranted.

References

On November 2, 2024, 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,” “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.

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.