Medical Policy Reference Manual
Medical Policy

11.01.053 Measurement of Antibodies to biological agents such as Infliximab and Adalimumab

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Description

Infliximab (Remicade®, Janssen Biotech) and adalimumab (Humira®, AbbVie Inc.) are examples of genetically engineered monoclonal antibodies that block the action of tumor necrosis factor (TNF), a cytokine that leads to systemic inflammation. It is indicated for moderate to severe autoimmune diseases that have become refractory to conventional immunomodulation treatment, including rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis and ulcerative colitis.

Over long-term use, some patients may develop antibodies to these anti-TNF agents, also known as human anti-chimeric antibodies (HACA) that may neutralize their anti-inflammatory effect. A loss of response to infliximab or adalimumab has been observed in some patients, and the development of antibodies has been suggested as responsible. Levels of these antibodies can be measured in the laboratory using either a radioimmunoassay (RIA), enzyme-linked immunoabsorbent assay (ELISA) methods, or most recently, the homogenous mobility shift assay (HMSA). The latter method is able to measure antibody levels in the presence of serum infliximab or adalimumab, whereas infliximab or adalimumab interferes with the antibody measurement when the other two assays are used.

Assays of anti-infliximab antibodies or anti-adalimumab antibodies have been proposed for patients who have undergone prolonged treatment with infliximab or adalimumab and would benefit from continuation of TNF inhibition, particularly those who demonstrated a treatment response initially but now have reduced or no response to treatment.

Patients with a reduced response to biological agents may be treated by altering the dosage schedule, increasing the dosage, or switching to another biologic therapy. Infliximab, Adalimumab, certolizumab pegol, Vedolizumab, Natalizumab and Ustekinumab are examples of biologic therapies.

Policy

Measurement of anti-drug antibodies in patients receiving biologic therapies (e.g., Infliximab, Adalimumab, certolizumab pegol, Vedolizumab and Natalizuma and Ustekinumab), either alone or in combination with the measurement of serum biologic therapy levels is considered **experimental / investigational** as it does not meet TEC criteria #2-5.

Policy Guidelines

Rationale:

1. The technology must have final approval from the appropriate U.S.government regulatory bodies:

There is no approval required for laboratories that measure anti-infliximab antibodies or serum infliximab levels. Laboratories using standard or home-developed methods are regulated by the Clinical Laboratories Improvement Amendments (1988).

2. The scientific evidence must permit conclusions concerning the effect on health outcomes:

In three of the reviewed studies, approximately 50% of the tests provided inconclusive results due to the presence of infliximab in the blood, which interfered with the assay. One study used the RIA method using a technique to reduce or eliminate interference by serum infliximab. The two largest studies and two smaller studies found that treatment efficacy was not significantly reduced in patients that had anti-infliximab antibodies. Three studies found that the presence of anti-infliximab antibodies was associated with an increase in infusion reactions. However, in the largest of these studies the positive predictive value was determined to be low, and the author concluded that antibody testing would likely not provide information that would minimize infusion reactions. A research group conducted a retrospective review of medical records of 155 patients and assessed the clinical utility of 177 tests. The authors reported that the results impacted treatment decisions in 73%. In HACA-positive patients, changing to another anti-TNF agents was associated with a complete or partial response in 92%. The authors concluded that measurement of HACA and infliximab concentrations is clinically useful. However, additional, prospective studies are needed to establish the role of testing for antibodies testing and therapeutic infliximab levels.

3. The technology must improve the net health outcome:

Testing for anti-infliximab antibodies poses no risk in itself. However, the evidence does not permit conclusions regarding net health outcomes.

4. The technology must be as effective as any established alternatives:

Patients typically are managed based on response to infliximab. If an adverse reaction occurs, the treatment can be discontinued. For patients who are no longer responding to infliximab, and who have not had an adverse reaction, dose escalation is considered. One study reported that dose escalation was effective in 86% of the studied population based on a retrospective review of records. Also, the anti-TNF treatment can be changed to another agent, such as adalimumab (Humira®, Abbott Laboratories) or etanercept (Enbrel®, Immunex Corp.). Finally, another option would be to prevent formation of anti-infliximab antibodies by using an adjunctive immunosuppressant such as methotrexate or corticosteroids.

5. The improvement must be attainable outside the investigational settings:

Improvements in net health outcomes have not been established in the investigational settings. Therefore, it is not known whether net improvement outside the investigational settings is possible.

Update 2014:

The homogenous mobility shift assay (HMSA) has emerged as the preferred method for testing the presence of antibodies to the TNF inhibitors infliximab and adalimumab. Up to 40% of patients treated with the anti-TNF agents develop a reduced response to the drug's therapeutic effect, requiring dose adjustment to maintain a clinical response. In some cases, the reduced response is attributable to the development of antibodies, but not always. In addition, the presence of antibodies to TNF inhibitors does not always lead to reduced drug response. This may be explained by factors such as the antibodies' binding capacity or their affinity for non-functional portions of the drug molecule. The development of antibodies is seen more often in patients receiving episodic infusions as opposed to those receiving regular maintenance infusions. Loss of drug response is managed by dose escalation, shortening of the interval between infusions, adding an immunomodulator adjunct such as methotrexate, or by changing to another drug regimen.

The literature now consists of a number of prospective studies involving patients with inflammatory bowel disease (IBD) including Crohn's disease (CD) and ulcerative colitis (UC). The drug with the most study data is infliximab, used either alone or in conjunction with methotrexate. Laboratory methods included ELISA, radioimmunoassay, and HMSA. Most of the data were extracted from randomized trials, the design of which were not optimized for determining if measurement of antibodies is useful for guiding patient management. Most of the published studies were sponsored by Janssen Biotech or its predecessor, Centocor, Inc. Evidence was conflicting with respect to the association of antibodies with clinical response. One study that used HMSA established a relationship between antibody titer and response to infliximab. Of four studies that utilized ELISA one noted a relationship between the presence of anti-infliximab antibodies and treatment response, but three other studies using ELISA did not show such a relationship. Four studies reached conclusions that treatment response was related to trough levels of infliximab.

One study reported values for sensitivity and specificity. This single-center cohort study included 85 CD patients and 21 with UC for whom levels of infliximab and anti-infliximab antibodies were measured. Optimal cutoff values were determined separately for each disease using a receiver operating characteristic calculation. For CD the test yielded 81% sensitivity, and 94% specificity. For UC the sensitivity was 80% and the specificity 100%.

Studies have focused mainly on performance characteristics of the test using currently available assessment techniques, which have yielded results that at times are conflicting. Further studies are needed to establish patient selection criteria, optimal dosage management, adjunctive immunosuppression, and patient outcomes. Based on this evidence the policy remains experimental / investigational for testing of antibodies to and serum levels of both infliximab and adalimumab.

Update 2017:

A search of the peer-reviewed literature was performed for the period of November 2014 through February 2017. Findings in the literature do not change the conclusions on the use of anti-biological agent antibody measurement in a patient receiving biological agent treatment such as Infliximab and adalimumab. Therefore, the policy remains experimental / investigational.

Update 2018:

The policy statements were revised to include the measurement of anti-drug antibodies in other biological therapy agents (e.g., Infliximab, Adalimumab, certolizumab pegol, Vedolizumab and Natalizumab and Ustekinumab). The measurement of anti-drug antibodies in patients receiving biologic therapies either alone or in combination with the measurement of serum biologic therapy levels is considered **experimental / investigational**.

Update 2019:

A search of the peer-reviewed literature was performed for the period of March 2017 through March 2019. Findings in the literature do not change the conclusions on the measurement of anti-drug antibodies in patients receiving biologic therapies (e.g., Infliximab, Adalimumab, certolizumab pegol, Vedolizumab and Natalizumab and Ustekinumab), either alone or in combination with the measurement of serum biologic therapy. Therefore, the policy statement remains unchanged.

Update 2021:

A search of the peer-reviewed literature was performed for the period of March 2019 through March 2021. Findings in the literature do not change the conclusions on the measurement of anti-drug antibodies in patients receiving biologic therapies (e.g., Infliximab, Adalimumab, certolizumab pegol, Vedolizumab and Natalizumab and Ustekinumab), either alone or in combination with the measurement of serum biologic therapy. Therefore, the policy statement remains unchanged.

References

The following were among the resources reviewed and considered in developing this policy. By reviewing and considering the resources, CareFirst does not in any way endorse the contents thereof nor assume any liability or responsibility in connection therewith. The opinions and conclusions of the authors of these resources are their own and may or may not be in agreement with those of CareFirst.

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