Clinical Policy Title: Measurement of serum antibodies to infliximab and adalimumab

Clinical Policy Number: 01.01.03

Effective Date: January 1, 2016
Initial Review Date: September 16, 2015
Most Recent Review Date: October 19, 2016
Next Review Date: October 2017

Related policies:
None.

ABOUT THIS POLICY: Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Keystone First when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First’s clinical policies are not guarantees of payment.

Coverage policy

Keystone First considers the measurement of serum antibodies to the drugs infliximab and adalimumab, taken either alone or in combination, to be investigational and, therefore, not medically necessary.

Limitations:

Note: The following CPT/HCPCS codes are not listed in the Pennsylvania Medicaid fee schedule:

83516 - Immunoassay for analyte other than infectious agent antibody or infectious agent antigen antigen; qualitative or semiquantitative, multiple step method

83520 - Immunoassay for analyte other than infectious agent antibody or infectious agent antigen antigen; quantitative, not otherwise specified

Alternative covered services:
None.

**Background**

Infliximab (Remicade®, Janssen) is an intravenous tumor necrosis factor alpha blocking agent. Adalimumab (Humira®, AbbVie) is a subcutaneous tumor necrosis factor alpha inhibitor. Each is used 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.

About one-third of patients receiving these drugs do not respond to therapy, and more experience a waning in response after initial success. Therefore, it is important to have accurate results of levels of antibodies that are often associated with nonresponse or temporary response.

Antibodies to infliximab (ATI) and antibodies to adalimumab (ATA) are measures of antibodies that indicate levels of clinical response to infliximab and adalimumab. ATI and ATA measures are not comparable across assays, and thus are not able to discern the effects of the medications on patients who showed improvement, and those whose benefits have been found to wane over time in a substantial proportion of cases.

In their efforts to develop treatment modes to standardize results among patients taking infliximab and adalimumab, practitioners have collected information on serum levels of antibodies to these drugs. However, standardization remains elusive.

**Searches**

Keystone First searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on September 19, 2016. Search terms were: “serum antibodies” AND “infliximab” AND “adalimumab.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple
cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

Findings

Researchers have struggled to develop an effective and consistent means of measuring serum antibody levels ATI and ATA. 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 ATI and ATA 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).

ATA and ATI 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 ATI in patients with irritable bowel syndrome ranging from 22 percent to 46 percent, but authors concluded that the true incidence of ATI after infliximab is unknown “due to the different administration schedules, timing of ATI measurements, methods used in ATI detection, and the presence of serum infliximab” (Nanda, 2013).

Another meta-analysis showed that in 18 studies of 3,326 patients given infliximab, ATI antibodies to the drug was prevalent in just 45.8 percent and 12.4 percent given episodic infusions and maintenance treatments, respectively. The authors conclude that patients who test positive for ATI have an elevated risk of infusion reactions, but the same risk of remission as do patients testing negative for ATI (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 ATI varied by study, with a high of 25.3 percent. However, fewer than half of the studies were rated as good quality (Thomas, 2015). A 2015 systematic review also found varying levels of ATI presence by study, and a link between presence of ATI 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).

Policy updates:
The 2016 update has added four peer-reviewed references, three of which are recent meta-analyses included in the summary of clinical evidence section.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meroni (2015)</td>
<td><strong>Key points:</strong></td>
</tr>
</tbody>
</table>
| Patterns of antibody presence and response to treatment | - Meta-analysis of 57 studies of infliximab (n=34), adalimumab (n=18), etanercept (n=5).  
- Most patients had irritable bowel disease or rheumatoid arthritis.  
- The presence of ATI linked with lower levels of infliximab and reduced disease control/remission.  
- Authors cite lack of homogeneity in study design or methodology, along with varied assays. |
| Thomas (2015)                     | **Key points:**                   |
| Risk of antibodies in various disorders | - Meta-analysis of 68 studies of patients with rheumatoid arthritis (n=8766), irritable bowel syndrome (n=4351), or spondyloarthopathies (n=1534).  
- 32 of 68 studies were of good quality.  
- Presence of antidrug antibody linked with reduced response for most drugs and conditions.  
- Prevalence of antidrug antibody varied by study, no higher than 25.3%. |
| Lee (2012)                        | **Key points:**                   |
| Prevalence of antidrug antibodies | - Meta-analysis of 18 studies (n=3326) patients with inflammatory bowel disease. Prevalence of ATI 45.8% when episodic infusions of infliximab were given. Prevalnce of ATI 12.4% when maintenance infusions of infliximab were given. |
| National Institute for Health and Clinical Excellence (2012) | **Key points:**                   |
|                                  | - Management of Crohn’s disease.  
- No recommendations for antidrug antibody testing with tumor necrosis factor inhibitors. |
| American College of Gastroenterology (2008) | **Key points:**                   |
- No recommendations for antidrug antibody testing with tumor necrosis factor inhibitors. |

**Glossary**

**Adalimumab** — A subcutaneous tumor necrosis factor (TNF) anti-inflammatory drug, also known as Humira.

**Humira** — See “Adalimumab.”

**Infliximab** — An intravenous tumor necrosis factor alpha blocking agent used against autoimmune disease, also known as Remicade.

**Remicade** — See “Infliximab.”
**Tumor necrosis factor (TNF) alpha blocking agents** — Drugs that block tumor necrosis factor, cytokines that can cause cell death.

**References**

**Professional society guidelines/other:**


**Peer-reviewed references:**


**Clinical trials:**

Searched clinicaltrials.gov on September 20, 2016, using terms “measurement infliximab antibodies” and “measurement adalimumab antibodies.” | Open Studies. 17 studies found (11 infliximab, 6 adalimumab), none relevant.

**CMS National Coverage Determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

No NCDs identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comments</th>
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<tbody>
<tr>
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<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquanitative, multiple step method</td>
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<td>Code</td>
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<td>83520</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious</td>
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<td></td>
<td>agent antigen; quantitative, not otherwise specified</td>
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<td>86335</td>
<td>Immunofixation electrophoresis, other fluids with concentration (e.g., urine,</td>
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<td>CSF)</td>
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