Measurement of Serum Antibodies to Infliximab, Adalimumab, Ustekinumab, and Vedolizumab

Effective: October 1, 2019

Next Review: April 2020
Last Review: August 2019

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Antidrug antibodies to infliximab, adalimumab, ustekinumab, and vedolizumab may be found in patients undergoing treatment for inflammatory bowel disease, psoriasis, or rheumatoid arthritis and are thought to be associated with a loss of treatment response.

MEDICAL POLICY CRITERIA

Measurement of antibodies to infliximab, adalimumab, ustekinumab, or vedolizumab, either alone or as a combination test which includes the measurement of medication serum levels, is considered investigational.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Medication Policy Manual. Note: Do a find (Ctrl+F) and enter drug name in the find bar to locate the appropriate policy.
BACKGROUND

INFLIXIMAB, ADALIMUMAB, USTEKINUMAB, AND VEDOLIZUMAB IN AUTOIMMUNE DISEASE

Therapy with monoclonal antibodies has revolutionized treatment of patients with inflammatory diseases such as inflammatory bowel disease (IBD; Crohn’s disease [CD] and ulcerative colitis [UC]), rheumatoid arthritis and psoriasis. These agents are generally given to patients who fail conventional medical therapy, and they are typically highly effective for induction and maintenance of clinical remission. However, not all patients respond, and a high proportion of patients lose response over time. An estimated one-third of patients do not respond to induction therapy (primary nonresponse), and 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).[1]

Infliximab (Remicade®, Janssen Biotech) is an intravenous tumor necrosis factor alpha (TNFα) blocking agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis, CD, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and ulcerative colitis (UC). Infliximab is a chimeric (mouse/human) anti-TNFα monoclonal antibody. Adalimumab (Humira® AbbVie) is a subcutaneous TNFα inhibitor that is FDA-approved for treatment of the above indications (CD and UC in adults only) plus juvenile idiopathic arthritis (JIA). Adalimumab is a fully human monoclonal antibody to TNFα. Vedolizumab (Entyvio®, Millennium Pharmaceuticals) is an intravenous blocking agent for integrin α4β7 and is FDA-approved for adults with CD or UC. Ustekinumab (Stelara®, Janssen Biotech) is an antibody that blocks interleukins IL-12 and IL-23 and is FDA-approved to treat psoriasis and certain patients with Crohn’s disease.

Following primary response to these medications, some patients become nonresponders (secondary nonresponse). The development of ADA is thought to be a cause of secondary nonresponse. ADA are also associated with injection site reactions (adalimumab), and acute infusion reactions and delayed hypersensitivity reactions (infliximab). As a fully human antibody, adalimumab is considered less immunogenic than chimeric antibodies, such as infliximab.

DETECTION OF ANTIDRUG ANTIBODIES

The detection and quantitative measurement of ADA has been fraught with difficulty owing to drug interference and identifying when antibodies are likely to have a neutralizing effect. First-generation assays, (i.e., enzyme-linked immunosorbent assays [ELISA]) can measure only ADA in the absence of detectable drug levels, due to interference of the drug with the assay. Other techniques available for measuring antibodies include the radioimmunoassay (RIA) method, and more recently, the homogenous mobility shift assay (HMSA) using high-performance liquid chromatography. Disadvantages of the RIA method are associated with the complexity of the test and prolonged incubation time, and safety concerns related to the handling of radioactive material. The HMSA has the advantage of being able to measure ADA when infliximab is present in the serum. A reporter-gene assay (RGA) is also available, which allows for the measurement of ADAs capable of neutralizing drug activity.[2] Cell-based assays typically have difficulty in standardization, take up to two days to complete, and with effects from the serum matrix. However, the RGA can quantify the antidrug neutralizing antibody
independent of matrix effects within two hours. Application of the RGA has recently been assessed for use in a clinical laboratory setting, and found to be a precise and high-throughput robust platform for detection of ADA.[3] Large randomized studies are still necessary to establish relevant clinical cut-off levels. Studies evaluating the validation of results among different assays are lacking, making inter-study comparisons difficult. One retrospective study in 63 patients demonstrated comparable diagnostic accuracy between two different ELISA methods in patients with IBD (i.e., double antigen ELISA and antihuman lambda chain-based ELISA).[4] This study did not include an objective clinical and endoscopic scoring system for validation of results. A review by Seow and Panaccione, noted that the variability and lack of standardization in current assay tests has important implications for subsequent studies which report associations between antibodies-to-infliximab (ATIs) and infliximab levels and utilize these assays to predict treatment response.[5] These findings highlight the need for a validated gold standard test and established diagnostic parameters with which to measure levels of infliximab and ATIs.

TREATMENT OPTIONS FOR PATIENTS WITH SECONDARY LOSS OF RESPONSE TO ANTI-TNF THERAPY

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

REGULATORY STATUS

Prometheus® Laboratories Inc., a College of American Pathologists–accredited lab under CLIA, offers non-radiolabeled fluid-phase HMSA tests called the Anser® IFX test for infliximab. Anser® ADA for adalimumab, Anser® UST for ustekinumab, and Anser® VDZ for vedolizumab. None of these tests are ELISA-based and they can measure antidrug antibodies in the presence of detectable drug levels, improving upon a major limitation of the ELISA method. All tests measure serum concentrations and antidrug antibodies.

These tests were developed and validated by Prometheus Laboratories Inc. They have not been cleared or approved by the U.S. Food and Drug Administration (FDA).

EVIDENCE SUMMARY

Validation of the clinical use of any diagnostic test focuses on analytic validity, diagnostic validity, and clinical utility. Analytic validity demonstrates technical feasibility as compared to a gold standard, including assessment of test reproducibility and precision. For comparison among studies, a common standardized protocol is necessary. Diagnostic utility is evaluated by the ability of a test to accurately predict the clinical outcome in appropriate populations of patients. For accurate interpretation of study results, sensitivities, specificities, and positive and negative predictive values compared to a gold standard must be known. Clinical utility is established when the evidence demonstrates that the diagnostic information obtained from a test can be used to benefit patient management and improve health outcomes. This evidence review focuses on the clinical validity and clinical utility.

Most studies evaluating antibodies to infliximab, adalimumab, ustekinumab, or vedolizumab report serum drug together with antidrug antibody (ADA) levels, and correlate levels to disease response. Serum drug levels and disease response will not be addressed in this section and
therefore the data reported on ADA will be highlighted from the identified studies. Most evidence concerning testing for ADA is derived from the data available for patients with inflammatory bowel disease (IBD) and rheumatoid arthritis (RA). Less literature exists concerning other diseases comprising psoriasis and spondyloarthropathies (SpA; i.e., ankylosing spondylitis, psoriatic arthritis, IBD-associated arthritis, reactive arthritis, and undifferentiated and juvenile SpA). There is also a lack of literature on the measurement of anti-vedolizumab and anti-ustekinumab antibodies for patient management.

CLINICAL VALIDITY

There is a substantial body of evidence examining associations of ADA with nonresponse and injection or infusion site reactions; numerous systematic reviews and meta-analyses have been published. Accordingly, the review of evidence concerning clinical validity focuses on the most current systematic reviews (see Tables 3 through 5) and studies published since those reviews,[6] as well as relevant studies not included in identified reviews (e.g., those focusing on adverse reactions and ADA).

Systematic Reviews

Six systematic reviews published from 2012 through 2017 were identified.[7-11] The number of studies included ranged from 11[10] to 68,[11] varying according to review objectives and conditions of interest. Although not detailed here, there was considerable overlap in included studies across reviews.

A systematic review and meta-analysis by Pecoraro (2017) selected 34 studies (total n=4,273 patients), including randomized controlled trials (RCTs, n=4), prospective observational (n=22), retrospective observational (n=6), and cross-sectional (n=2).[12] Studies evaluated RA (n=18), ulcerative colitis (n=2), CD (n=5), psoriatic arthritis (n=4), ankylosing spondylitis (n=5), plaque psoriasis (n=4), spondyloarthritis (n=1). Most of the patients (45%) received infliximab, 35% received adalimumab, and 21% received etanercept. None received golimumab or certolizumab. Reviewers identified studies published through August 2016 and rated study quality as good (n=17), fair (n=16), and poor (n=1). The effect of ADA was evaluated in 19 studies, showing a significant (p<0.05) reduction of response (relative risk [RR] 0.43, 95% confidence interval [CI] 0.3 to 0.63) in ADA-positive patients relative to ADA-negative patients, with adalimumab therapy demonstrating a greater reduction (RR 0.40, 95% CI 0.25 to 0.65, p<0.001) than infliximab (RR 0.37, 95% CI 0.2 to 0.7, p<0.001). Measures of heterogeneity were 84%, 57%, and 79%, respectively. Fourteen studies reported on the effect of ADA on clinical response (see Table 1). Eleven studies found the risk of developing ADA to be significantly (p=0.03) lower in patients treated with concomitant methotrexate therapy relative to treated those without methotrexate (RR 0.65, 95% CI 0.47 to 0.9). Studies comparing treatment response with nonresponse (n=15) found responders (n=15) found responders to have a significantly (p<0.001) lower risk of developing ADA relative to nonresponders (RR 0.31, 95% CI 0.18 to 0.52). The presence of ADA was associated with a significant reduction of anti-tumor necrosis factor α (TNF-α) serum concentration (see Table 2). Of the 20 studies (n>2,800 patients) reporting data on adverse events, 31% (n=2 studies) developed infections, 18% (n=12 studies) developed injection-site reactions, 8% (n=11 studies) discontinued treatment due to adverse events, and 5% (n=1 study) developed serious adverse events (5%). Although ADA significantly reduced TNF-α response, the results should be viewed cautiously due to reported study limitations, including small numbers of studies included and considerable heterogeneity.
A systematic review and meta-analysis by Thomas (2015) included 68 studies (14,651 patients) with patients with RA (n=8,766), SpA (n=1,534), and IBD (n=4,351) and examined the immunogenicity of infliximab (39 comparisons), adalimumab (15), etanercept (5), golimumab (14), and certolizumab (8). The review identified studies published through December 2013 and included 38 RCTs and 30 observational studies (study quality rated as good [n=32], moderate [n=26], or poor [n=10]). The pooled prevalence of ADA varied with disease and drug (see Table 3, highest with infliximab: 25.3%). Duration of exposure (reported in 60 studies) was examined for its potential effect on the development of ADA and most studies employed ELISA assays. The presence of ADA was associated with lower odds of response across most drugs and diseases (see Table 4). An exception was in studies of IBD (similar to that reported by Lee [2012]). The use of immunosuppressive agents substantially decreased the risk of ADA (odds ratio [OR] 0.26, 95% CI 0.21 to 0.32). Finally, infusion reactions and injection site reactions were more common (see Table 5) when ADA were detectable (OR 3.25, 95% CI 2.35 to 4.51). Evaluation of potential publication bias or overall assessment (e.g., GRADE or similar) for the body of evidence was not reported. Additionally, no measures of heterogeneity were reported.

A systematic review by Meroni (2015) included 57 studies of infliximab (n=34), adalimumab (n=18), and etanercept (n=5). Studies included primarily patients with IBD and RA, but also SpA and psoriasis. Most studies were prospective cohort designs (n=42) and a formal assessment of study quality (bias) was not reported. The authors noted considerable variability in the time from drug administration to ADA and drug bioavailability testing across studies. Varied antibody testing assay methods were used and included solid-phases RIA, traditional ELISA, fluid-phase RIA, and bridging ELISA; cutoffs for positive test results were also inconsistently reported. The ranges of patients with detectable ADA varied substantially (see Table 3) but were consistent with other reviews. Qualitatively, the presence of ADA was associated with lower levels of infliximab and lower risk of disease control or remission. The presence of ADA also increased the risk of infusion reactions. When ascertained, the time to development of ADA varied from as little as 16 weeks to over a year. The time to ADA positivity varied – fifty percent of patients with detectable ADA at 28 weeks to a median time of one year. Finally, for both infliximab and adalimumab, immunosuppression was associated with less ADA positivity. The authors concluded that “…the lack of homogeneity in study design and methodologies used in the studies analyzed limited the opportunity to establish the time-course and clinical consequences of anti-drug antibody development....” Although qualitative, the authors included many studies, and provided a detailed review of each study not reported by the other meta-analyses. The author’s conclusions are consistent with the meta-analyses but with emphasis on important aspects of heterogeneity across studies.

Hsu (2014) published a systematic review of ADA in psoriasis that included 25 studies (n=7,969) with at least 15 patients. Ten of these studies reported on infliximab ADA: three found an association between ADA and lower serum infliximab levels, and five found an association between ADA and clinical response. Of the five studies that evaluated antiadalimumab antibodies, four found lower treatment efficacy for those with ADA. Six studies reported on ustekinumab ADA, and two of these found an associating between ADA and Psoriasis Area and Severity Index (PASI) response. The remaining six studies in the review focused on antietanercet antibodies.

Nanda (2013) conducted a meta-analysis of studies that reported on clinical outcomes according to the presence or absence of ADA in patients with IBD. MEDLINE, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Scopus
databases were searched to February 2012, EMBASE to August 2012; 11 studies involving 707 patients were included. Six of these studies (two RCTs, one prospective cohort study, three retrospective cohort studies) were included in the meta-analysis by Lee (2012) outlined below. In at least one quality domain (study eligibility criteria, measurement of exposure and outcome, control for confounders, completeness of follow-up), all the included studies had high risk of bias. The prevalence of detectable ADA in the included studies ranged from 22.4% to 46% (see Table 3). The outcome of interest was loss of response to infliximab, defined as “relapse of clinical symptoms in patients who were in clinical remission from, or had responded to, infliximab.” Measures of loss of response varied across studies and included clinician assessment, standardized scales (Crohn’s Disease Activity Index [CDAI], Harvey-Bradshaw Index, Simple Clinical Colitis Activity Index), and requirement for surgery or presence of nonhealing fistula. Patients with ATIs had a three-fold greater risk of loss of response than those without ATIs (RR 3.2, 95% CI 2.0 to 5.0) (shown in Table 3 as the RR of clinical response in treated vs. untreated patients to allow comparison with other meta-analyses). This result was influenced primarily by 532 patients with CD (RR 3.2, 95% CI 1.9 to 5.5); pooled results for 86 patients with ulcerative colitis (UC) were not statistically significant (pooled RR 2.2, 95% CI 0.5 to 9.0). Eighty-nine patients with unspecified IBD also were included in the meta-analysis. In addition to potential bias in included studies and heterogeneity in outcome assessment, the meta-analysis is limited by variability in the method of ADA detection (double-antigen ELISA, antihuman lambda chain-based ELISA, fluid-phase RIA). Study investigators stated, “[t]he true incidence of ADA in IBD patients treated with infliximab remains unknown due to the different administration schedules, timing of ADA measurements, methods used in ADA detection, and the presence of serum infliximab.” Finally, although the authors noted that the funnel plot “suggested the presence of publication bias,” the small number of studies and plot appearance (only 2 of 11 studies suggesting asymmetry) preclude conclusions.

Garces (2013) performed a meta-analysis of studies of infliximab and adalimumab used to treat RA, IBD, SpA, and psoriasis.[8] Databases were searched to August 2012, and 12 prospective cohort studies included involving 860 patients (540 with RA, 132 with SpA, 130 with IBD, 58 with psoriasis). The outcome of interest was response, assessed by using standard assessment scales for rheumatologic diseases (e.g., European League Against Rheumatism criteria for RA; Assessment in Ankylosing Spondylitis 20% response criteria, or ASDAS for spondyloarthritis; Psoriasis Area and Severity Index for psoriasis) and clinician assessment for IBD. Overall, detectable ADA were associated with a 68% reduction in drug response (pooled RR=0.32, 95% CI 0.22 to 0.48). Significant heterogeneity was introduced by varying use of immunosuppressant therapy (e.g., methotrexate) across studies. To assess ADA, most studies used RIA, which is less susceptible than ELISA to drug interference and may be more accurate.

Lee (2012) conducted a meta-analysis of patients with IBD receiving infliximab to estimate the prevalence of ADA, effect of ADA on the prevalence of infusion reactions, and the effect of ADA on disease remission rates.[9] Databases were searched through October 2011, and 18 studies involving 3,326 patients were included. Studies included nine RCTs, five prospective cohort studies, and four retrospective cohort studies. The prevalence of ADA was 45.8% when episodic infusions of infliximab were given and 12.4% when maintenance infliximab was given (see Table 3). Patients with ADA were less likely to be in clinical remission (Table 4), but this was not statistically significant (RR, 0.90, 95% CI 0.79 to 1.02, p=0.10). The rates of infusion reactions were significantly higher in patients with ADA (RR 2.07 [see Table 5], 95% CI 1.61 to 2.67). Immunosuppressants resulted in a 50% reduction in the risk of developing ADA (p<0.001). The meta-analysis concluded that patients with IBD who test positive for ATIs are at
an increased risk of infusion reactions, but have similar rates of remission compared with patients who test negative for ATIs.

Table 1. Effect of Antidrug Antibodies on Clinical Response

<table>
<thead>
<tr>
<th>Outcome Measures</th>
<th>No. Studies</th>
<th>MD</th>
<th>95% Confidence Interval</th>
<th>$I^2$, %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Activity Score 28</td>
<td>9</td>
<td>0.93</td>
<td>0.41 to 1.44</td>
<td>84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BASDAI</td>
<td>2</td>
<td>-0.62</td>
<td>-1.51 to 0.27</td>
<td>0</td>
<td>0.17</td>
</tr>
<tr>
<td>ASDAS</td>
<td>2</td>
<td>0.96</td>
<td>-0.27 to 2.2</td>
<td>0</td>
<td>0.13</td>
</tr>
<tr>
<td>Psoriasis Area Severity Index</td>
<td>1</td>
<td>4.7</td>
<td>-1.15 to 9.25</td>
<td>NR</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Adapted from Pecoraro (2017).[12]
ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; $I^2$: heterogeneity measure; MD: mean difference; NR: not reported.

Table 2. Evaluation of Anti-TNF-α Concentration

<table>
<thead>
<tr>
<th>Outcome Measures</th>
<th>No. Studies</th>
<th>MD, mg/L</th>
<th>95% Confidence Interval</th>
<th>$I^2$, %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA-positive vs ADA-negative</td>
<td>8</td>
<td>-7.07</td>
<td>-8.9 to -5.25</td>
<td>98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Responders vs no responders</td>
<td>13</td>
<td>2.77</td>
<td>1.97 to 3.58</td>
<td>82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adalimumab therapy</td>
<td>6</td>
<td>5.07</td>
<td>3.77 to 6.36</td>
<td>62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infliximab</td>
<td>4</td>
<td>2.74</td>
<td>0.59 to 4.89</td>
<td>62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Etanercept</td>
<td>3</td>
<td>0.85</td>
<td>0.41 to 1.13</td>
<td>82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DAS28 change from baseline</td>
<td>8</td>
<td>-2.18</td>
<td>-2.91 to -1.44</td>
<td>97</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Adapted from Pecoraro (2017).[12]
ADA: antidrug antibodies; DAS28: Disease Activity Score in 28 joints; $I^2$: heterogeneity measure; MD: mean difference; TNF: tumor necrosis factor.

Table 3. Estimated Prevalence of Antidrug Antibodies from Meta-Analyses[14]

<table>
<thead>
<tr>
<th>Author</th>
<th>Included Studies</th>
<th>Drugs</th>
<th>Disease</th>
<th>Prevalence of ADA</th>
<th>Pooled (95% CI)</th>
<th>Range in Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IFX</td>
<td>ADL</td>
<td>Other^</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee (2012)</td>
<td>18^b</td>
<td>•</td>
<td>•</td>
<td>^</td>
<td>20.8% (19.2 to 22.5)</td>
<td>Episodic</td>
</tr>
<tr>
<td>Episodic Maintenance</td>
<td>5</td>
<td>•</td>
<td>•</td>
<td></td>
<td>45.8% (41.7 to 50.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>•</td>
<td>•</td>
<td></td>
<td>12.4% (10.8 to 14.1)</td>
<td></td>
</tr>
<tr>
<td>Nanda (2013)</td>
<td>11</td>
<td>•</td>
<td></td>
<td></td>
<td>22.4%-46%</td>
<td></td>
</tr>
<tr>
<td>Thomas (2015)</td>
<td>39^c</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>25.3% (19.5 to 32.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15^e</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>6.9% (3.4 to 13.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>15.8% (9.6 to 24.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>12.1% (8.1 to 17.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>•</td>
<td>•</td>
<td></td>
<td>8.9% (3.8 to 19.2)</td>
<td></td>
</tr>
<tr>
<td>Meroni (2015)</td>
<td>14</td>
<td>•</td>
<td></td>
<td>•</td>
<td>19%-47%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>•</td>
<td></td>
<td></td>
<td>15%-61%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>•</td>
<td></td>
<td>•</td>
<td>26%-50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>•</td>
<td></td>
<td>•</td>
<td>5%-54%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>•</td>
<td></td>
<td>•</td>
<td>9%-46%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>•</td>
<td></td>
<td>•</td>
<td>18%-45%</td>
<td></td>
</tr>
</tbody>
</table>

ADL: adalimumab; CI: confidence interval; IBD: inflammatory bowel disease; IFX: infliximab; RA: rheumatoid arthritis; SpA: spondyloarthritis.
^ Includes etanercept, golimumab, certolizumab.
^ Includes three studies including both maintenance and episodic therapy
^ Number of comparisons in table; did not report studies for pooled prevalence.
^ Also psoriasis.
Table 4. Results from Meta-Analyses of Antidrug Antibodies and Clinical Response[14]

<table>
<thead>
<tr>
<th>Author</th>
<th>Included Studies</th>
<th>Drugs</th>
<th>Disease</th>
<th>Clinical Response: ADA vs None</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IFX</td>
<td>ADL</td>
<td>Othera</td>
</tr>
<tr>
<td>Lee (2012)</td>
<td>18</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Nanda (2013)</td>
<td>11</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Garces (2013)</td>
<td>12</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Thomas (2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

ADL: adalimumab; CI: confidence interval; IBD: inflammatory bowel disease; IFX: infliximab; NR: not reported; OR: odds ratio; RA: rheumatoid arthritis; RR: relative risk; SpA: spondyloarthropathy.

a Includes etanercept, golimumab, certolizumab.
b Also psoriasis.

Table 5. Increased Risk of Adverse Reaction Associated With the Presence of Antidrug Antibodies[14]

<table>
<thead>
<tr>
<th>Author</th>
<th>Included Studies</th>
<th>Drugs</th>
<th>Disease</th>
<th>Adverse Reactions: ADA vs None</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IFX</td>
<td>ADL</td>
<td>Othersa</td>
</tr>
<tr>
<td>Lee (2012)</td>
<td>18</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Thomas (2015)</td>
<td>NR</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
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ADL: adalimumab; CI: confidence interval; IBD: inflammatory bowel disease; IFX: infliximab; NR: not reported; OR: odds ratio; RA: rheumatoid arthritis; RR: relative risk; SpA: spondyloarthropathy.
a Infusion reaction.

Nonrandomized Studies

Recent publications not included in the systematic reviews above are included, below.

Van den Berghe (2018) published a small study evaluating ADA to vedolizumab in a cohort of 40 patients with IBD.[15] This study included the development of an ELISA-based test to measure ADA in the presence of the drug. Antivedolizumab antibodies and vedolizumab trough levels were measured after six weeks of treatment and after treatment discontinuation. At the six-week follow-up, three (8%) of the patients were positive for ADA, but this appeared to be transient. None of the patients who discontinued vedolizumab were positive for ADA at the time of their last infusion or after discontinuation. The authors concluded that immunogenicity did not appear to play a major role in vedolizumab treatment failure.

Cludts (2017) conducted a single-center retrospective cohort analysis of patients with RA (n=18), psoriatic arthritis (n=9), or ankylosing spondylitis (n=12) in Italy.[16] Serum samples were taken prior to adalimumab therapy and after 12 and 24 weeks of treatment. Psoriatic arthritis and ankylosing spondylitis patients were grouped together (SpA) due to axial involvement in all psoriatic arthritis patients. Although adalimumab levels varied among patients (0 to 30 µg/mL), median levels were significantly lower at 12 and 24 weeks in ATA-positive samples, and antibody formation was associated with decreasing levels of circulating adalimumab. A reporter gene assay detected neutralizing antibodies against TNF antagonists in ATA-positive, therapeutic-negative patients; however, neutralization could not be confirmed in all ATA-positive samples due to adalimumab interference. There was a negative correlation between ADA levels and adalimumab in all groups, with 43.6% and 41% of the adalimumab-treated patients developing antibodies at 12 and 24 weeks, respectively.
These percentages increased to 48.7% and 46% after subjecting the samples to acid treatment. There was a negative correlation between adalimumab trough levels and DAS28 and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores (p<0.001). There were no significant differences between BASDAI in ATA-positive compared with ATA-negative patients at 12 or 24 weeks. The study is consistent with others suggesting that adalimumab levels can serve as an indicator of ATA; however, limitations included small sample size, retrospective research design, and failure to confirm neutralization in all ATA-positive samples.

Using an observational, cross-sectional study design, Ara-Martin (2017) analyzed the impact of immunogenicity on response to anti-TNF therapy in 137 adults with moderate-to-severe plaque psoriasis at 35 centers in Spain between 2012 and 2014.[17] All patients experienced secondary nonresponse to adalimumab (n=65), etanercept (n=47), and infliximab (n=19) after six or more months of treatment. Serum ADA was identified in 48%, 0%, and 42% of patients of patients treated with adalimumab, etanercept, and infliximab, respectively. Loss of efficacy was assessed using the PASI (PASI >5), 75% improvement in PASI score from baseline (PASI75), and/or the Physician Global Assessment (PGA, >2). PGA values for ADA-positive vs ADA-negative patients were significantly worse in the adalimumab group (3.7 vs 3.2, p=0.02) but not in the infliximab group. There was a significant negative linear correlation between serum drug concentrations and ADA in both the adalimumab group (p=0.001) and among the three groups combined (p=0.001), and a significant (p=0.019) correlation between serum ADA titer and body surface area. Unlike the other studies, in this study, the use of concomitant antirheumatic drugs was not associated with anti-TNF immunogenicity in any of the groups. This study provided evidence of antibody development against adalimumab and infliximab (not against etanercept) in patients with psoriasis, with ADA formation accounting for half of the secondary nonresponse associated with these therapies. However, conclusions were limited due to the cross-sectional study design, use of ELISA to detect ADAs due to drug interference, the potential presence of neutralizing antibodies as confounding factors, and limited information about patients’ health status prior to the study period.

A case-control, longitudinal study by Lombardi (2016) excludes possible confounding factors by analyzing adalimumab treatment for psoriasis in five distinct groups, including individuals who received: biologic therapies after switching from adalimumab (n=20); ongoing adalimumab therapy (n=30); novel adalimumab therapy (n=30); biologic therapies other than adalimumab (n=15); and no treatment with immunosuppressants or biologics (n=15), serving as a quasi-control.[18] The clinical severity of psoriasis was scored using the PASI. At 12-month follow-up, ADA was highest (87%) in patients who received biologic therapies after switching from adalimumab. The false-positive rate was 23% for adalimumab detection and 22% for anti-adalimumab antibodies in individuals who were never treated with adalimumab. There was no significant difference in median PASI score between the anti-adalimumab antibody-negative patients (1.1) and the anti-adalimumab antibody-positive patients (4.0). There was no association between PASI score or TNF-α concentration and the presence of anti-adalimumab antibodies in patients receiving adalimumab. Additionally, there were no significant differences in TNF-α and C-reactive protein concentrations. Study limitations included its observational design, small sample size, use of ELISA to measure ADA, and high variability of results. The authors concluded that the assay has limited clinical utility.

Chiu[19] (2015) published a prospective observational study investigating the role of ustekinumab ADA in psoriasis. The study included 76 individuals with plaque psoriasis who were treated with ustekinumab for at least seven months (mean 13 months). Antibodies to ustekinumab were found in five (6.5%) of the patients, and the presence of these antibodies
was associated with lower serum levels of the drug (p<0.001) and lower PASI 50 response (p=0.004). Among the 15 patients who switched to ustekinumab from adalimumab, no difference in ustekinumab ADA was found between patients who had previously developed adalimumab ADA and those who did not.

Menting (2015) reported on the association between serum ustekinumab trough levels, ADA, and treatment efficacy in a small prospective study that included 41 patients with RA.[20] The mean follow-up time was 32 weeks (range 4 to 52 weeks), and during this period ADA to ustekinumab were detected in three patients. No correlations were seen between ustekinumab trough levels and clinical response to the medication.

While many studies have evaluated clinical validity using single ADA measurements, at least one study assessed their persistence over time. Vande Casteele (2013) analyzed infliximab trough and ADA levels using an HMSA assay with banked serum obtained from 90 IBD patients treated between May 1999 and August 2011.[21] ADA levels had been previously assayed using an ELISA-based test. A total of 1,232 samples were evaluated (mean 14 per patient). Treatment decisions were made solely on clinical evaluation and C-reactive protein levels. ADA were detected in 53 of 90 (59%) of patients but subsequently were nondetectable in 15 of the 53 (28%). Persistent ATIs were associated with discontinuation of infliximab (RR 5.1, 95% CI 1.4 to 19.0), but the wide confidence interval reflects considerable uncertainty. Although transience of ADA in IBD has not been carefully scrutinized, if replicated, these results suggest interpreting a single ADA result cautiously.

Section Summary

A large body of evidence has evaluated the clinical validity of ADA testing. ADA has been associated with secondary nonresponse in RA, SpA, but not clearly in IBD. The presence of ADA has been consistently associated with an increased risk of infusion-site reaction related to infliximab and injection site reactions related to adalimumab. A concomitantly administered immunosuppressant agent reduces the risk of developing ADA.

CLINICAL UTILITY

Several algorithms have been developed for management of patients with IBD[22-24] or RA[25] who have relapsed during TNF-inhibitor therapy. These algorithms are generally based on evidence that has indicated an association between ADA, reduced serum drug levels, and relapse. None has included evidence demonstrating improved health outcomes, such as reduced time to recovery from relapse (response), using algorithmic rather than dose-escalation approaches.

In a study of patients with IBD, Fernandex (2019) compared proactive monitoring of infliximab ADA and trough levels (n=56) to a retrospective control cohort (n=149).[26] The primary outcomes were hospital admission, surgery, treatment discontinuation, and rates of mucosal healing. A composite “unfavorable outcome” comprised of all of these was also analyzed. There was an association between treatment escalation rates and proactive monitoring (60.7% vs. 16.8% of controls, p<0.001). After two years of follow-up, surgery rates were lower in the proactive group (8.9% vs. 20.8%, p=0.030) and mucosal healing was more common (73.2% vs. 38.9%, p<0.0001). No significant differences were seen in hospitalization rate or treatment discontinuation.
A similar retrospective study by Papamichael (2019) evaluated proactive monitoring of serum adalimumab levels and ADA (n=53) with standard of care, defined as empirical dose escalation (n=279) or reactive monitoring (n=50). Patients with early treatment failure (within eight weeks) were not included. After a median follow up of 3.1 years, fewer patients in the proactive monitoring group experienced treatment failure (hazard ratio [HR] 0.4, 95% CI 0.2 to 0.9). No significant difference was found for the probability of IBD-related surgery.

Afif (2010) evaluated the clinical utility of measuring ADA (referred to as human antichimeric antibodies [HACA] in the study) and infliximab concentrations by retrospectively reviewing patient medical records. Record review from 2003 to 2008 identified 155 patients who had ADA, had data on infliximab concentrations, and met the study inclusion criteria. A single physician ordered 72% of the initial tests. The authors retrospectively determined clinical response to infliximab. Forty-seven percent of patients were on concurrent immunosuppressive medication. The main indications for testing were loss of response to infliximab (49%), partial response after initiation of infliximab (22%), and possible autoimmune or delayed hypersensitivity reaction (10%). ADA were identified in 35 (23%) patients and therapeutic infliximab concentrations in 51 (33%) patients. Of 177 tests assessed, the results impacted treatment decisions in 73%. In ATI-positive patients, change to another anti-TNF agent was associated with a complete or partial response in 92% of patients, whereas dose escalation occurred in 17%.

The authors concluded that measurement of ADA and infliximab concentration had a clinically useful effect on patient management. The strategy of increasing infliximab dose in patients with ADA was ineffective whereas in patients with subtherapeutic infliximab concentrations this strategy was a good alternative to changing to another anti-TNF agent. Study limitations included the retrospective design and using ELISA testing for ADA. Because there was no control group, one cannot determine what changes in management would have been made absent ADA measurement. Because clinicians are likely to change management for patients who do not achieve or maintain a clinical response, it is important to understand how these management decisions differ when ADA are measured.

Steenholdt (2014) reported results of a noninferiority trial and cost-effectiveness analysis of 69 patients with CD who relapsed (CDAI ≥220 and/or ≥1 draining perianal fistula) during infliximab therapy. Patients were randomized to infliximab dose intensification (5 mg/kg every four weeks) or algorithmic treatment based on serum infliximab level and ATI: Patients with subtherapeutic infliximab level (<0.5 μg/mL) had infliximab dose increased if ADA were undetectable or were switched to adalimumab if ADA were detectable; patients with therapeutic infliximab level underwent repeat testing of infliximab and ADA levels if ADA were detectable or diagnostic reassessment if ADA were undetectable. Serum infliximab and ADA levels were measured in all patients using RIA in single-blind fashion (patients unaware but investigators aware of test results). Randomized groups were similar at baseline; overall, 55 (80%) of 69 patients had nonfistulizing disease. Most patients (70%) had therapeutic serum infliximab levels without detectable ATI; revised diagnoses in 6 (24%) of 25 such patients in the algorithm arm included bile acid malabsorption, strictures, and IBS. In both intention-to-treat (ITT) and per-protocol analyses, similar proportions of patients in each randomized group achieved clinical response at week 12, defined as a minimum 70-point reduction from baseline CDAI for patients with nonfistulizing disease and a minimum 50% reduction in active fistulas for patients with fistulizing disease (ITT 58% in the algorithm group vs 53% in the control group, p=0.810; per-protocol, 47% in the algorithm group vs 53% in the control group.
Conclusions on the noninferiority of an algorithmic approach compared with dose intensification from this trial are limited. The noninferiority margin was arguably large and was exceeded in the conservative per-protocol analysis. Dropouts were frequent and differential between groups; 17 (51%) of 33 patients in the algorithm group and 28 (78%) of 36 patients in the control group completed the 12-week trial. A large proportion of patients (24%) in the algorithmic arm were potentially misdiagnosed (i.e., CD flare was subsequently determined not to be the cause of relapse); the comparable proportion in the control arm was not reported. In most patients (80% who had nonfistulizing disease), only a subjective measure of treatment response was used (minimum 70-point reduction from baseline CDAI).

Roblin (2014) conducted a single-center, prospective observational study of 82 patients with IBD (n=45 CD, n=27 UC) with clinical relapse (CDAI >220 or Mayo Clinic >5) during treatment with adalimumab 40 mg every two weeks. For all patients, trough adalimumab levels and ADA were measured in a blinded fashion using ELISA, and adalimumab dose was optimized to 40 mg weekly. Those who did not achieve clinical remission (CDAI <150 or Mayo score <2) within four months underwent repeat trough adalimumab and anti-adalimumab antibody testing and were switched to infliximab. Clinical and endoscopic responses after adalimumab optimization and after infliximab therapy for six months were compared across three groups: (1) those with a therapeutic adalimumab level (>4.9 μg/mL), (2) those with a subtherapeutic adalimumab level and undetectable ATA; and (3) those with a subtherapeutic adalimumab level and detectable ADA. After adalimumab optimization, more group 2 patients achieved clinical remission (16 [67%] of 24 patients) than group 1 (12 [29%] of 41 patients; p<0.01 vs group 2) and group 3 (2 [12%] of 17 patients, p<0.01 vs group 2) patients. Duration of remission was longest in group 2 (mean 15 months) compared with group 1 (mean five months) and group 3 (mean, four months, p<0.01 for both comparisons vs group 2). At one year, 13 (52%) of 24 patients in group 2 maintained clinical remission compared with no patients in groups 1 or 3 (p<0.01 for both comparisons vs group 2). Results were similar when remission was defined using calprotectin levels (<250 μg/g stool) or endoscopic Mayo score (<2).

Fifty-two patients (n=30 CD, n=22 UC) who failed to achieve clinical remission after adalimumab optimization were switched to infliximab. More patients in group 3 achieved clinical remission (12 [80%] of 15 patients) than in group 1 (2 [7%] of 29 patients) or group 2 (2 [25%] of 8 patients, p<0.01 for both comparisons vs group 3). Duration of response after switching to infliximab was longest in group 3 (mean, 14 months) compared with group 1 (mean, three months) and group 2 (mean, five months, p<0.01 for both comparison vs group 3). At one year, 8 (55%) of 15 patients in group 3 maintained clinical remission compared with no patients in groups 1 or 2 (p<0.01 for both comparisons vs group 3). Results were similar using objective measures of clinical remission (calprotectin level, endoscopic Mayo score).

These results suggested that patients with IBD who relapse on adalimumab and have subtherapeutic serum adalimumab levels may benefit from a higher adalimumab dose if ADA are undetectable or from a change to another TNF inhibitor if ADA are detectable. Relapsed patients who have therapeutic serum adalimumab levels may benefit from change to a different drug class. Strengths of the study include its use of subjective and objective measures of remission and blinded serum drug level and ADA monitoring. However, results were influenced by the small sample size, use of ELISA for antibody testing, and lack of ADA.
levels for decision making. Studies comparing management using the algorithm proposed with usual care are needed.

**PRACTICE GUIDELINE SUMMARY**

In 2017, the American Gastroenterological Association published an evidence-based clinical practice guideline on therapeutic drug monitoring (TDM) in inflammatory bowel disease (IBD). The guideline was developed according to the GRADE framework to evaluate certainty of evidence, and a Technical Review was published to accompany the recommendations. Regarding measurement of antidrug antibodies, the Association made the following statement:

“In adults with active IBD treated with anti-TNF agents, the AGA suggests reactive therapeutic drug monitoring to guide treatment changes.” *Conditional recommendation, very low quality of evidence.*

According to the GRADE method, *very low quality* is defined as: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

The guideline also stated:

“In adult patients with quiescent IBD treated with anti-TNF agents, the AGA makes no recommendation regarding the use of routine proactive therapeutic drug monitoring.” *No recommendation, knowledge gap.*

**SUMMARY**

Antibodies to infliximab or adalimumab are present in a substantial number of patients treated with these medications, and there may be a correlation between the level of these antibodies and clinical response. Antibodies to ustekinumab and vedolizumab have also been reported. However, there is not enough research to determine whether measurement of these antidrug antibodies can be used in patient management to improve net health outcomes. In addition, the optimal timing of when to measure antibody levels and measurement cutoff levels has not been established. Therefore, the measurement of antidrug antibodies to infliximab, adalimumab, ustekinumab, or vedolizumab is considered investigational.

**REFERENCES**

response to infliximab. Clinica chimica acta; international journal of clinical chemistry. 2016 Jan 30;453:147-53. PMID: 26689333


### CODES

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