



# MEASUREMENT OF SERUM ANTIBODIES TO INFLIXIMAB AND ADALIMUMAB (REQUIRES PREAUTHORIZATION)

V.21

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### DESCRIPTION

Infliximab (Remicade®; Janssen Biotech) is an intravenous tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) blocking agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis (RA), Crohn disease (CD), ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and ulcerative colitis. Adalimumab (Humira®; AbbVie) is a subcutaneous TNF- $\alpha$  inhibitor that is FDA-approved for treatment of these indications (CD and ulcerative colitis [UC] in adults only) and juvenile idiopathic arthritis. Following primary response to infliximab and adalimumab, some patients become nonresponders (secondary nonresponse). The development of antidrug antibodies (ADA) is considered to be a cause of secondary nonresponse.

The evidence for measuring anti-TNF- $\alpha$  inhibitor antibodies in patients who have rheumatoid arthritis, psoriatic arthritis, or juvenile idiopathic arthritis; inflammatory bowel diseases (Crohn disease, ulcerative colitis); ankylosing spondylitis; or plaque psoriasis includes multiple systematic reviews, a single randomized controlled trial, and other observational studies. Relevant outcomes are test accuracy and validity, change in disease status, health status measures, quality of life, and treatment-related morbidity. Antibodies-to-infliximab (ATI) or to adalimumab (ATA) develop in a substantial proportion of treated patients and are believed to neutralize or enhance clearance of the drugs. Considerable evidence demonstrates an association between ADA and secondary nonresponse as well as injection site and infusion reactions. The clinical usefulness of measuring ADA hinges on whether test results inform management changes, thereby leading to improved outcomes, compared with management directed by symptoms, clinical assessment, and standard laboratory evaluation. Limited evidence describes management changes after measuring ADA. A small, randomized controlled trial in patients with CD comparing ATI-informed management of relapse with standard



that are informative for discriminating treatment responses have not been established. The evidence is insufficient to determine the effects of the technology on health outcomes.

## Dates

Original Effective

**09-01-2015**

Last Review

**08-07-2024**

Next Review

**08-11-2025**

## POLICY

I. Measurement of antibodies to infliximab in a patient receiving treatment with infliximab, either alone or as a combination test, which includes the measurement of serum infliximab levels, is considered **Investigational**.

II. Measurement of antibodies to adalimumab in a patient receiving treatment with adalimumab, either alone or as a combination test, which includes the measurement of serum adalimumab levels, is considered **Investigational**.

III. Measurement of antibodies to vedolizumab in a patient receiving treatment with vedolizumab, either alone or as a combination test, which includes the measurement of serum vedolizumab levels, is considered **Investigational**.

## RECOMMENDED MEDICAL RECORDS

- History and Physical Report
- Office Notes

## BACKGROUND

### Infliximab and Adalimumab in Autoimmune Disease

Infliximab is a chimeric (mouse/human) anti-tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) monoclonal antibody. Adalimumab is a fully human monoclonal antibody to TNF- $\alpha$ . Therapy with monoclonal antibodies has revolutionized therapy in patients with inflammatory diseases such as inflammatory bowel disease (IBD; Crohn disease, ulcerative colitis),



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).<sup>1</sup> 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 likely have a neutralizing effect. First-generation assays, (ie, 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. Studies evaluating the validation of results among different assays are lacking, making interstudy comparisons difficult. One retrospective study in 63 patients demonstrated comparable diagnostic accuracy between 2 different ELISA methods in patients with IBD (ie, double antigen ELISA and antihuman lambda chain-based ELISA).<sup>2</sup> This study did not include an objective clinical and endoscopic scoring system for validation of results.

## 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 nonanti-TNF agent.



literature was searched through September 30, 2015 to identify literature assessing the analytic validity, clinical validity, and clinical utility of measuring serum antidrug antibodies (ADA). Most studies evaluating antibodies to infliximab or to adalimumab report serum drug together with ADA levels, and correlate levels to disease response. Serum drug levels and disease response will not be addressed in this evidence review and therefore the data reported on antidrug antibodies 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 spondyloarthropathies (SpA; eg, ankylosing spondylitis, psoriatic arthritis, IBD-related arthritis, reactive arthritis, some juvenile idiopathic arthritis) and psoriasis.

## Analytic Validity Measurement of Antibodies to Infliximab

Wang et al (2012) developed and validated a non-radiolabeled homogeneous mobility shift assay (HMSA) to measure antibodies-to-infliximab (ATI) and infliximab levels in serum samples.<sup>3</sup> Full method validation was performed on both the ATI- and infliximab-HMSA, and the clinical sample test results were compared with those obtained from a bridging enzyme-linked immunosorbent assay (ELISA) method to evaluate the difference in performance between the 2 assays. Intra- and interassay precision rates (as indicated by the coefficient of variation [CV]) for the ATI- and infliximab-HMSA were less than 4% and less than 15%, respectively, and less than 6% and less than 15%, respectively, considered to be robust.

Sera from 100 healthy subjects (blood bank donors) were tested to determine the assay cut points, defined to have an upper limit of approximately 97.5%. Using receiver operating characteristic analysis, a cut point of 1.19 µg/mL was calculated for ATI yielding a sensitivity of 95% (95% confidence interval [CI],

89 to 98) with a false-positive rate of 3%. For serum infliximab levels, a cut point of 0.98 µg/mL was calculated; the false-positive rate with this cut point was 5%. One hundred serum samples that previously had tested positive with ELISA were reanalyzed by the new method. There was a high correlation between the 2 methods for ATI levels ( $p < 0.001$ ). The new method identified 5 false-positive samples from the bridging ELISA method, thought to be due to a higher rate of nonspecific binding in the ELISA method.

In 2014, Steenholdt et al published a post hoc comparison of different ATI assays.<sup>4</sup> Blood samples were collected from 66 (96%) of 69 patients enrolled in a randomized controlled trial (RCT) (discussed next) that assessed algorithmic treatment for Crohn disease (CD) relapse during



by RIA, in 6 patients (9%) by ELISA, and in 22 patients (33%) by HMSA. The reporter gene assay detected anti-infliximab activity, most likely due to ATI, in 7 patients (11%). As observed by the authors, this suggests that ATI detected by RIA and HMSA are not necessarily functionally active or neutralizing. Five patients (8%) were ATI-positive and 43 patients (65%) were ATI-negative by all 4 assays. Correlations were statistically significant ( $p < 0.001$ ) in all pairwise comparisons ( $r$  range, 0.77 to 0.96). However, statistical agreement between assays could not be estimated accurately (eg, using the intraclass correlation coefficient) because different assays reported values on different arbitrary scales. Regardless of the assay used, most patients (74% to 88%) had therapeutic serum infliximab levels and undetectable ATI, suggesting nonpharmacologic reasons for relapse or for symptoms mimicking relapse.

## Measurement of Antibodies to Adalimumab

Wang et al (2013) developed and validated a nonradiolabeled HMSA to measure antibodies-toadalimumab (ATA) and adalimumab levels in serum samples.<sup>6</sup> Analytic validation of performance characteristics (ie, calibration standards, assay limits, intra- and interassay precision, linearity of dilution, substance interference) was performed for both the ATA- and adalimumab-HMSA. Because the elimination half-life of adalimumab (10-20 days) overlaps the dosing interval (every 2 weeks), ATApositive sera to provide calibration standards were difficult to collect from patients (ie, the drug-free interval for antibody formation is short). Therefore, antisera from rabbits immunized with adalimumab were pooled to form calibration standards. Serial dilutions of these ATA calibration standards then generated a standard curve against which test samples were compared. Over 29 experimental runs, intra-assay precision and accuracy for the adalimumab-HMSA (as indicated by the CV) were less than 20% and 3%, respectively; interassay (run-to-run, analyst-to-analyst, and instrument-to-instrument) precision and accuracy were less than 12% and less than 22%, respectively. For the ATA-HMSA, CVs for intra-assay precision and accuracy were less than 3% and 13%, respectively; CVs for interassay precision and accuracy were less than 9% and less than 18%, respectively. ELISA could not be used as a standard comparator due to competition from circulating drug.

Following evaluation of analytic validity of the non-radio-labeled HMSA assay, the investigators tested sera from 100 healthy subjects (obtained from blood bank donors) to determine the cut points of the assay, defined as the threshold above which samples were deemed to be positive with an upper limit of approximately 99%. The calculated cut point for serum adalimumab levels was 0.68  $\mu\text{g/mL}$ , which yielded a false-positive rate of 3%. For ATA, the calculated cut point was 0.55 U/mL, which yielded a falsepositive rate of 1%. Analysis of 100 serum samples from patients who were losing response to adalimumab showed that 44%



greater than 20 µg/mL, 18% were AIA-positive.

## Section Summary: Analytic Validity

Analytic validity of ATI testing by HMSA was demonstrated using ELISA as a standard comparator. Test performance characteristics were considered robust. However, a subsequent comparative study identified substantial variability across ATI assay methods using a functional cell-based assay as standard. The pharmacokinetic properties of adalimumab (long half-life relative to dosing interval) prevented use of ELISA as a standard comparator in tests of analytic validity of ATA. Test performance characteristics were determined by comparison to a standard curve generated by serial dilutions of pooled rabbit antisera. Lack of comparison to an alternative method of antibody detection raises uncertainty about the analytic validity of the ATA test. The commercial Prometheus® HMSA assays do not suffer from many of the technical performance limitations of older assays; however, the HMSA assays do not distinguish neutralizing and non-neutralizing antibodies.<sup>7</sup>

## 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 1 through 3) and studies published subsequent to the search dates of those reviews,<sup>8</sup> as well as relevant studies not included in identified reviews (eg, those focusing on adverse reactions and ADA).

## Systematic Reviews and Meta-Analyses

Five reviews published from 2012 through 2015 were identified.<sup>7,9-12</sup> The number of studies included ranged from 11<sup>11</sup> to 68,<sup>12</sup> varying according to review objectives and conditions of interest. Although not detailed here, there was considerable overlap in included studies across reviews.

Lee et al (2012) conducted a meta-analysis of patients with IBD receiving infliximab to estimate the prevalence of ATI, effect of ATI on the prevalence of infusion reactions, and the effect of ATI on disease remission rates.<sup>10</sup> Databases were searched through October 2011, and 18 studies involving 3326 patients were included. Studies included 9 RCTs, 5 prospective cohort studies, and 4 retrospective cohort studies. The prevalence of ATI was 45.8% when episodic infusions of infliximab were given and 12.4% when maintenance infliximab was given (see Table 1). Patients with ATI were less likely to be in clinical remission (Table 2), but this was not statistically significant (relative risk [RR], 0.90; 95% CI, 0.79 to 1.02; p=0.10). The rates of infusion reactions were significantly higher in patients with ATI (RR=2.07 [see Table



increased risk of infusion reactions, but have similar rates of remission compared with patients who test negative for ATIs.

Nanda et al (2013) conducted a meta-analysis of studies that reported on clinical outcomes according to the presence or absence of ATI in patients with IBD.<sup>11</sup> 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 (2 RCTs, 1 prospective cohort study, 3 retrospective cohort studies) were included in the meta-analysis by Lee et al. In at least 1 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 ATI in the included studies ranged from 22.4% to 46% (see Table 1). 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 3-fold greater risk of loss of response than those without ATIs (RR=3.2; 95% CI, 2.0 to 5.0) (shown in Table 1 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 ATI detection (double-antigen ELISA, antihuman lambda chain-based ELISA, fluid-phase RIA). Study investigators stated, "[t]he true incidence of ATI in IBD patients treated with infliximab remains unknown due to the different administration schedules, timing of ATI measurements, methods used in ATI 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 et al (2013) performed a meta-analysis of studies of infliximab and adalimumab used to treat RA, IBD, SpA, and psoriasis.<sup>9</sup> 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 (eg, European





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 (eg, methotrexate) across studies. To assess antidrug antibodies, most studies used RIA, which is less susceptible than ELISA to drug interference and may be more accurate.

A systematic review and meta-analysis by Thomas et al (2015)<sup>12</sup> included 68 studies (14,651 patients) in patients with RA ( $n=8766$ ), SpA ( $n=1534$ ), and IBD ( $n=4351$ ) 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 1, 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 2). An exception was in studies of IBD (similar to that reported by Lee et al). 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 3) when ADA were detectable (OR=3.25; 95% CI, 2.35 to 4.51). Evaluation of potential publication bias or overall assessment (eg, GRADE or similar) for the body of evidence was not reported. Additionally, no measures of heterogeneity were reported.

The systematic review by Meroni et al (2015)<sup>7</sup> searched PubMed through March 2013 and 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 1) but were consistent with other reviews.

Qualitatively, the presence of ATI was associated with lower levels of infliximab and lower risk of disease control or remission. The presence of ATI also increased the risk of infusion reactions. When ascertained, the time to development of ATI varied from as little as 16 weeks to over a year. The time to ATA positivity varied (eg, 50% of patients with detectable ATA at 28 weeks to a median time of 1 year). Finally, for both





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.

## Studies of Clinical Validity Published Subsequent to Searches of Systematic Reviews

Three recent publications not included in a systematic review were identified.<sup>13-15</sup> Results were consistent with conclusions of the systematic reviews.

Arstikyte et al<sup>13</sup> (2015) prospectively evaluated the association of ADA with adverse events, clinical response, and serum drug levels in 143 symptomatic patients (62 with RA, 81 with SpA; mean age 45 years [SD=13]) treated with TNF blockers in Lithuania. All patients receiving adalimumab or infliximab were tested and 1 of 3 patients was given etanercept (because it is more commonly used). A response in RA patients was defined as either good, moderate, or low according to EULAR criteria<sup>16</sup>; SpA disease activity was considered inactive, moderate, high, or very high according to established criteria,<sup>17</sup> with inactive and moderately active disease defined as response. At least 3 months after therapy initiation, a single serum sample was obtained prior to dosing between January 2012 and December 2013; disease activity and other patient characteristics (eg, symptom duration, health status) were assessed concurrently. Serum adalimumab, infliximab, and etanercept levels were obtained; ADA was assayed using a bridging ELISA. Of 57 patients receiving infliximab, 14 (24.6%) had detectable antibodies with 13 of the 14 undetectable infliximab trough levels. Disease activity at baseline was unassociated with the development of ADA in either disease. In patients achieving response, infliximab and adalimumab trough levels were higher, but not significantly ( $p=0.09$  and  $p=0.14$ , respectively). However, adalimumab concentrations were significantly higher in nonresponders ( $p<0.001$ ). Antibodies to infliximab were associated with infusion reactions but with little certainty (OR=5.9; 95% CI, 1.0 to 33.3) as was stopping infliximab treatment or changing agent. Study strengths include its prospective design, standardized assessments, and responder definition. Limitations involve the small number of nonresponders and no indication whether any eligible participants declined enrollment. Finally, the associations reported are consistent with other reports and ADA results were not apparently used in decision-making.

Frederiksen et al<sup>14</sup> (2014) conducted a single-center retrospective cohort study of IBD patients treated with infliximab ( $n=187$ ) or adalimumab ( $n=57$ ) in Denmark. ADA were assayed using fluid-phase RIA; 49% of



predictive value 0.91 (95% CI, 0.59 to 1.0), sensitivity 0.50 (95% CI, 0.27 to 0.73); negative predictive value 0.74 (95% CI, 0.57 to 0.87), specificity 0.97 (95% CI, 0.82 to 1.0) (with values varying according to adalimumab trough levels). The authors also reported that patients switching to adalimumab from infliximab who had antibodies were more likely to develop antibodies to adalimumab. These findings are consistent with other studies and evaluation of ADA using RIA (a strength of this study). However, its conclusions are limited by the retrospective nature and sample size.

Jani et al (2015)<sup>15</sup> measured ADA by RIA together with drug levels in 331 RA patients treated with adalimumab (n=160) and etanercept (n=171) between November 2008 and March 2013. Patients were participants in the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate conducted in 60 centers across the U.K. Disease activity was assessed using the Disease Activity Score in 28 joints (DAS28). A response was evaluated using EULAR response criteria or changed DAS28 score. Following 12 months of adalimumab therapy, ADA were detectable in 24.8% of patients (almost all were detectable by 6 months) and were associated with lower drug levels. Both routine (nontrough) drug levels and ATA were associated with DAS28 at 12 months. In predicting EULAR nonresponse, the AUC for adalimumab concentration less than 5 mg/mL at 3 months was 0.66 (95% CI, 0.55 to 0.77) and for presence of ADA was 0.68 (95% CI, 0.54 to 0.81). None of the etanercept patients developed detectable ADA. Although derived from a well-established observational study designed to examine predictors (genetic and other) of treatment response, ADA levels were not used to inform treatment decisions. These results corroborate other study findings.

While many studies have evaluated clinical validity using single ADA measurements, at least one study assessed their persistence over time. Vande Casteele et al (2013)<sup>18</sup> analyzed infliximab trough and ATI levels using an HMSA assay with banked serum obtained from 90 IBD patients treated between May 1999 and August 2011. ATI levels had been previously assayed using an ELISA-based test. A total of 1232 samples were evaluated (mean 14 per patient). Treatment decisions were made solely on clinical evaluation and C-reactive protein levels. ATI 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 ATI in IBD has not been carefully scrutinized, if replicated, these results suggest interpreting a single ATI result cautiously.

## Section Summary: Clinical Validity

A large body of evidence has evaluated the clinical validity of ADA testing. ADA has been associated with secondary nonresponse in RA,



concomitantly administered immunosuppressant agent reduces the risk of developing ADA.

## Clinical Utility

Several authors have published algorithms for management of patients with IBD<sup>19-21</sup> or RA<sup>22</sup> who relapse during TNF-inhibitor therapy. These algorithms are generally based on evidence, including that reviewed earlier, which indicate an association between antidrug antibodies, reduced serum drug levels, and relapse. None include evidence demonstrating improved health outcomes, such as reduced time to recovery from relapse (response), using algorithmic rather than dose-escalation approaches.

Afif et al (2010) evaluated the clinical utility of measuring ATI (referred to as human antichimeric antibodies [HACA] in the study) and infliximab concentrations by retrospectively reviewing the medical records of patients with IBD who had had ATI and infliximab concentrations measured. The study sought to determine whether these results affected clinical management.<sup>23</sup> Medical record review from 2003 to 2008 identified 155 patients who had had ATI and infliximab concentrations measured and who met the study inclusion criteria. A single physician ordered Seventy-two percent 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/delayed hypersensitivity reaction (10%). ATI were identified in 35 patients (23%) and therapeutic infliximab concentrations in 51 patients (33%). 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 had a response of 17%.

The authors concluded that measurement of ATI and infliximab concentration impacted management and was clinically useful. Increasing the infliximab dose in patients with ATI was ineffective, whereas in patients with subtherapeutic infliximab concentrations, this strategy was considered a good alternative to changing to another anti-TNF agent.<sup>23</sup> Limitations to the study included its retrospective design and that the testing for antibodies to infliximab was performed using the enzyme-linked immunosorbent assay (ELISA) method. Because there was no control group in this study, it is not possible to determine what changes in management would have been made in the absence of ATI measurement. Clinicians are likely to make some changes in management for patients who do not achieve or maintain a clinical response, and it is important to understand how these management decisions differ when ATI are measured.

In 2014, Steenholdt et al reported results of a noninferiority trial and costpatients with CD who relapsed (CDAI  $\geq 220$  and/or  $\geq 1$  draining perianal fistula) during infliximab therapy. Patients were randomized to infliximab dose intensification (5 mg/kg every 4 weeks) or algorithmic treatment based on serum infliximab level and ATI: Patients with subtherapeutic infliximab level ( $<0.5 \mu\text{g/mL}$ <sup>24</sup>) had infliximab dose increased if ATI were undetectable or were switched to adalimumab if ATI were detectable; patients with therapeutic infliximab level underwent



(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<sup>25</sup> included bile acid malabsorption, strictures, and IBS. In both intention-to-treat 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 (intention-to-treat: 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;  $\chi^2$  test,  $p=0.781$ ). Only the intention-to-treat analysis fell within the prespecified noninferiority margin of -25% for the difference between groups.

Conclusions concerning 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 (ie, 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 et al (2014) conducted a single-center, prospective observational study of 82 patients with IBD ( $n=45$  CD,  $n=27$  UC) with clinical relapse ( $\text{CDAI} > 220$  or Mayo Clinic  $> 5$ ) during treatment with adalimumab 40 mg every 2 weeks.<sup>26</sup> 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 ( $\text{CDAI} < 150$  or Mayo score  $< 2$ ) within 4 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 6 months were compared among 3 groups: (1) those with therapeutic adalimumab level ( $> 4.9 \mu\text{g/mL}$ <sup>27</sup>), (2) those with subtherapeutic adalimumab level and undetectable ATA; and (3) those with subtherapeutic adalimumab level and detectable ATA. After adalimumab optimization, more group 2 patients achieved clinical remission (16 [67%] of 24 patients) compared with 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). Duration of remission was longest in group 2 (mean [SD], 15 [5] months) compared with group 1



patients in group 1 or group 3 ( $p < 0.01$  for both comparisons vs group 2). Results were similar when remission was defined using calprotectin levels ( $< 250 \mu\text{g/g}$  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) compared with group 1 (2 [7%] of 29 patients) and group 2 (2 [25%] of 8 patients;  $p < 0.01$  for both comparisons vs group 3). Duration of response after switch to infliximab was longest in group 3 (mean [SD], 14 [7] months) compared with group 1 (mean [SD], 3 [2] months) and group 2 (mean [SD], 5 [3] months; log-rank test,  $p < 0.01$  for both comparison vs group 3). At 1 year, 8 (55%) of 15 patients in group 3 maintained clinical remission compared with no patients in group 1 or group 2 ( $p < 0.01$  for both comparisons with group 3). Results were similar using objective measures of clinical remission (calprotectin level and endoscopic Mayo score).

These results suggest that patients with IBD who relapse on adalimumab and have subtherapeutic serum adalimumab levels may benefit from increased adalimumab dose if ATA are undetectable or change to another TNF-inhibitor if ATA are detectable. Relapsed patients who have therapeutic serum adalimumab levels may benefit from change to a different drug class. Strengths of the study are use of both subjective and objective measures of remission and blinded serum drug level and ATA monitoring. However, results are limited owing to the small sample size, use of ELISA for antibody testing, and lack of ADA levels for decision making. Subsequent study comparing the management using the algorithm proposed with usual care is needed. Ideally, more than one method of antibody assay would be used to further assess analytic validity. Finally, the first author of the paper received lecture fees from the ADA test provider (Theradiag).

## Section Summary: Clinical Utility

Convincing evidence for the clinical utility of ADA testing currently is lacking. Uncontrolled retrospective studies in IBD demonstrate impacts of ADA testing on treatment decisions but cannot demonstrate improved patient outcomes compared with a no-testing strategy. Additional limitations of these studies include lack of clinical follow-up after treatment decisions were made (in Afif<sup>23</sup>) and use of clinical assessments to guide treatment decisions (in Steenholdt<sup>24</sup>). Additionally, determination of a clinically relevant threshold for ADA level is complicated by the use of various assay methods. A small, nonrandomized prospective study suggested that ADA levels may be informative in relapsed patients with IBD who have low serum adalimumab levels, but this finding requires confirmation in larger, randomized trials. Methodological flaws, including relapse



infliximab infusion and adalimumab injection site reactions, whether testing for ADA can reduce that risk is unclear. For example, Lichtenstein et al (2013)<sup>21</sup> conducted a systematic review of infliximab-related infusion reactions and concluded "...there is a paucity of systematic and controlled data on the risk, prevention, and management of infusion reactions to infliximab." They added that "[m]ore randomised controlled trials are needed in order to investigate the efficacy of the proposed preventive and management algorithms."

## Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 4.

**Table 4. Summary of Key Trials**

NCT No. Enrollment	Trial Date		
<b>Ongoing</b>			
<b>Rheumatoid arthritis</b>			
NCT01638715	A Randomized, Multi-Center Biomarker Trial to Predict Therapeutic Responses of Patients With Rheumatoid Arthritis to a Specific Biologic Mode of Action	200	Jun 2017
<b>Spondyloarthropathies</b>			
NCT01895764	Effect of the Combination of Methotrexate and Adalimumab on Reduction of Immunization in Ankylosing Spondylitis (COMARIS)	110	Apr 2015
NCT01971918	Comparative Analysis of Two Therapeutic Strategies in Patients With 104 Nov 2016 Spondyloarthritis Treated With Anti-TNF Biologics (STRADA)		

NCT: national clinical trial.

## Summary of Evidence

The evidence for measuring anti-TNF- $\alpha$  inhibitor antibodies in patients who have rheumatoid arthritis, psoriatic arthritis, or juvenile idiopathic arthritis; inflammatory bowel diseases (Crohn disease, ulcerative colitis); ankylosing spondylitis; or plaque psoriasis includes multiple systematic reviews, a single randomized controlled trial, and other observational studies. Relevant outcomes are test accuracy and validity, change in disease status, health status measures, quality of life, and treatment-related morbidity. Antibodies-to-infliximab (ATI) or to adalimumab (ATA) develop in a substantial proportion of treated patients and are believed to neutralize or enhance clearance of the drugs. Considerable evidence demonstrates an association between ADA and secondary nonresponse as well as injection site and infusion reactions. The clinical usefulness of measuring ADA hinges on whether test results inform management changes, thereby leading to improved outcomes, compared with management directed by symptoms, clinical assessment, and standard laboratory evaluation. Limited evidence describes management changes after measuring ADA. A small, randomized controlled trial in patients with CD comparing ATI-informed management of relapse with standard dose



that are informative for discriminating treatment responses have not been established. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Use this feature to find out if a procedure and diagnosis code pair will be approved, denied or held for review. Simply put in the procedure code, then the diagnosis code, then click "Add Code Pair". If the codes are listed in this policy, we will help you by showing a dropdown to help you.

### Procedure

Enter at least the first 3 characters of the code

### Diagnosis

Enter at least the first 3 characters of the code

## CODES

+ CPT4

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## REVISIONS

**04-26-2024**

Policy criteria reviewed - no changes. References updated.

**04-01-2022**

Added 83520 effective 4/1/2022

**03-01-2022**

Added codes 80145, 80230, 80280

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