



Kansas City

An Independent Licensee of the Blue Cross and Blue Shield Association

Measurement of Serum Antibodies to Infliximab and Adalimumab

Policy Number: 2.04.84
Origination: 2/1/2013

Last Review: 12/2013
Next Review: 12/2014

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for measurement of serum antibodies to Infliximab. This is considered investigational.

When Policy Topic is covered

Not Applicable

When Policy Topic is not covered

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**.

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**.

Considerations

According to materials from Prometheus on Anser™ IFX, it will be reported using CPT code 84999 (unlisted chemistry procedure).

Description of Procedure or Service

Infliximab (Remicade®, Janssen Biotech) is an intravenous tumor necrosis factor (TNF) alpha blocking agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis, Crohn's disease, 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 the above indications (Crohn's disease and ulcerative colitis in adults only) plus juvenile idiopathic arthritis. Secondary loss of response to infliximab and adalimumab is seen in a certain percentage of patients; the development of antidrug- antibodies has been suggested as one reason for nonresponse.

Background

Infliximab and adalimumab in autoimmune disease

Infliximab is a chimeric (mouse/human) anti-tumor necrosis factor (TNF)-alpha monoclonal antibody. Adalimumab is a fully human monoclonal antibody to TNF-alpha. Therapy with monoclonal antibodies has revolutionized therapy in patients with immune diseases such as inflammatory bowel disease (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 reason for therapeutic failures remains a matter of debate. One proposed factor associated with loss of response is the production of

antidrug antibodies, which accelerate clearance of the drug. (1) Antidrug antibodies also have been associated with acute infusion reactions (both drugs) and with 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 antidrug antibodies has been fraught with difficulty. First-generation assays, (i.e., enzyme-linked immunosorbent assays [ELISA]) can only measure antidrug antibodies in the absence of detectable drug levels due to interference of the drug with the assay, limiting clinical utility. 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 antidrug antibodies when infliximab is present in the serum. Studies evaluating the validation of the results between different assays are lacking, making interstudy comparisons difficult. One retrospective study in 63 patients demonstrated comparable diagnostic accuracy between 2 different ELISA methods, i.e., double antigen ELISA and antihuman lambda chain ELISA. (2) 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 non-anti-TNF agent.

Regulatory Status

Prometheus® Laboratories Inc. offers nonradiolabeled, fluid-phase HMSA tests called Anser™IFX for infliximab and Anser™ADA for adalimumab. Neither test is ELISA based, and each can measure antidrug antibodies in the presence of detectable drug levels, improving upon a major limitation of the ELISA method. Both tests measure serum drug concentrations and antidrug antibodies.

These tests were developed and their performance characteristics determined by Prometheus Laboratories Inc. Neither has been cleared or approved by the U.S. Food and Drug Administration.

Prometheus Laboratories Inc. is a CAP-accredited Clinical Laboratory Improvement Amendment (CLIA) laboratory.

Rationale

Literature Review

This policy was created in 2012 and is based on a search of the MEDLINE database through July 2013. Literature that describes the analytic validity, clinical validity, and clinical utility of measuring serum antidrug antibodies was sought. Most studies of antibodies to infliximab or to adalimumab report on both serum drug levels, as well as levels of antidrug antibodies, and correlate these levels to response rates of disease. Serum drug levels and disease response will not be addressed in this policy and therefore the data reported on antidrug antibodies will be highlighted from the aforementioned studies.

Most of the data on the use of measurements of antidrug antibodies are from patients with inflammatory bowel disease, with limited literature for other diseases such as rheumatoid arthritis.

Analytic and clinical validation

Measurement of antibodies to infliximab

Wang and colleagues developed and validated a non-radiolabeled homogeneous mobility shift assay (HMSA) to measure the antibodies-to-infliximab (ATI) and infliximab levels in serum samples. (3) 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 ELISA method to evaluate the difference in performance between the 2 assays. Intra- and inter-assay precision rates (as indicated by the coefficient of variation [CV]) for the ATI- and infliximab-HMSA were <4% and <15%, respectively, and <6% and <15%, respectively, considered to be robust.

Sera from 100 healthy subjects (obtained from blood bank donors) were tested to determine the cut points of the assay, defined to have an upper negative limit of approximately 97.5%. Using receiver operating characteristic analysis, a cut point of 1.19 µg/mL was calculated for ATI; the false positive rate with this cut point was 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.

A systematic review of the literature up to October 2008 by Cassinotti and Travis was undertaken to determine whether ATI have any clinical importance for infliximab efficacy or safety. (4) The authors offered the following findings from their review: that the biological and clinical mechanisms of ATI development are poorly understood, that the incidence of ATI in vivo depends on multiple analytical and clinical factors (both patient- and treatment-related), that the presence of ATI is weakly and variably associated with clinical response and infusion reactions (but not with reactions relevant to clinical decision making), and that enormous variation in the methods of reporting ATI and immunogenicity of infliximab make almost any comparison between studies (few with clinical relevance) impossible. Conclusions of the systematic review were that there was no clear evidence that ATI have an impact on efficacy or safety, nor is there a need to measure or prevent them in clinical practice.

A meta-analysis by Lee and colleagues was conducted in patients with inflammatory bowel disease (IBD) receiving infliximab to determine: the prevalence of ATI, the effect of ATI on the prevalence of infusion reactions, and the effect of ATI on disease remission rates. (5) Databases were searched through October 2011, and 18 studies involving 3,326 patients were included. Studies included 9 randomized controlled trials (RCTs), 5 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. The rates of infusion reactions were significantly higher in patients with ATI (relative risk [RR]: 2.07; 95% confidence interval [CI]: 1.61–2.67). Immunosuppressants resulted in a 50% reduction in the risk of developing ATI ($p < 0.001$). Patients with ATI were less likely to be in clinical remission, but this was not statistically significant (RR: 0.90; 95% CI: 0.79–1.02; $p = 0.10$). The meta-analysis concluded that patients 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.

Nanda and colleagues conducted a meta-analysis of studies that reported on clinical outcomes according to the presence or absence of ATI in patients with inflammatory bowel disease (IBD). (6) Databases were searched to February 2012 or later, and 11 studies involving 707 patients were included. Six of these studies (2 RCTs, 1 prospective cohort study, and 3 retrospective cohort studies) were included in the meta-analysis by Lee, described above. All included studies had high risk of bias in at least one quality domain (study eligibility criteria, measurement of exposure and outcome, control for confounders, and completeness of follow-up). 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 non-healing fistula.

Patients with ATIs had a 3-fold greater risk of loss of response than those without ATIs (pooled risk ratio [RR]: 3.2 [95% CI: 2.0–5.0]). This result was driven primarily by 532 patients with Crohn's disease (pooled RR: 3.2 [95% CI: 1.9–5.5]); pooled results for 86 patients with ulcerative colitis were not statistically significant (pooled RR: 2.2 [95% CI: 0.5–9.0]). (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 heterogeneity in the method of ATI detection (double-antigen ELISA, antihuman lambda chain ELISA, and fluid-phase RIA). Study investigators state, "The 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, a funnel plot suggested the presence of publication bias.

An "ambispective" analysis enrolled 94 patients (some analyzed retrospectively, some enrolled prospectively) who were treated with infliximab at a single institution for spondyloarthritis (50 ankylosing spondylitis, 12 undifferentiated spondyloarthritis, 22 psoriatic arthritis, and 10 IBD-associated spondyloarthritis). (7) Disease activity was measured every 6 months using the Ankylosing Spondylitis Disease Activity Score (ASDAS), and patients were monitored for ATI development (by bridging ELISA) and infusion reactions. During a mean duration of follow-up of 7 years, 25.5% of patients developed ATI. At 6 months, 1 year, and >4 years, ASDAS scores were higher (indicating more severe disease) in patients with ATI than in patients without ATI. Of 11 patients who developed infusion reactions, ATI were present in 8 (73%). Mean ATI titers were higher in patients who had infusion reactions than in those who did not ($p=0.028$). ATIs developed more commonly in patients who did not receive concomitant methotrexate (34.5% vs. 11.1%, $p=0.011$). A limitation of the study is that serum samples were not collected from all patients at each of the 3 time points studied (6 months, 1 year and >4 years); serum samples were obtained from 56 patients immediately after beginning treatment, from 9 patients during the first year of treatment, and from 29 patients after the first year of treatment.

Measurement of antibodies to adalimumab

Wang and colleagues developed and validated a non-radiolabeled HMSA to measure antibodies-to-adalimumab (ATA) and adalimumab levels in serum samples.(8) Analytic validation of performance characteristics (calibration standards, assay limits, intra- and inter-assay precision, linearity of dilution, and 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), ATA-positive sera to provide calibration standards were difficult to collect from human patients. (The drug-free interval for antibody formation is small.) 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 coefficient of variation [CV]) was <20% and <3%, respectively; inter-assay (run-to-run, analyst-to-analyst and instrument-to-instrument) precision and accuracy were <12% and <22%, respectively. For the ATA-HMSA, CVs for intra-assay precision and accuracy were <3% and <13%, respectively; CVs for inter-assay precision and accuracy were <9% and <18%, respectively. ELISA could not be used as a standard comparator due to competition from circulating drug.

Sera from 100 healthy subjects (obtained from blood bank donors) were tested to determine the cut points of the assay, defined as the threshold above which samples were deemed to be positive with an upper negative 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 false positive rate of 1%.

Analysis of 100 serum samples from patients who were losing response to adalimumab showed that 44% were above the cut point for ATA, and 26% were below the cut point for serum adalimumab level. In samples below the adalimumab cut point (0.68 $\mu\text{g/mL}$), 68% were ATA positive; in samples with adalimumab levels >20 $\mu\text{g/mL}$, 18% were ATA-positive.

Korswagen and colleagues reported on 3 patients (2 with rheumatoid arthritis and 1 with psoriatic arthritis) who developed severe venous and arterial thromboembolic events during treatment with adalimumab.(9) All 3 patients had ATA detected using radioimmunoassay (RIA). The authors conducted a retrospective search for thromboembolic events among 272 consecutive patients with rheumatoid arthritis treated with adalimumab at a single institution in The Netherlands. Arterial thromboembolic events were defined as myocardial infarction, cerebrovascular accident, transient ischemic attack, peripheral arterial thrombosis, and small-vessel occlusion. Venous thromboembolic events were defined as deep vein thrombosis with or without pulmonary embolism, superficial vein thrombosis, and thrombosis at unusual sites. Serum samples were collected at baseline and just before adalimumab injection at 1, 3, and 6 months after baseline and every 6 months thereafter. Eight thromboembolic events were found, 4 of which occurred in patients with ATA. Incidence rates were 26.9/1,000 person-years for patients with ATA and 8.4/1,000 person-years for patients without ATA. Unadjusted hazard ratio (HR) was 3.8 (95% CI: 0.9–15.3), $p=0.064$; adjusted (for duration of follow-up, age, body mass index, erythrocyte sedimentation rate, and previous thromboembolic events) HR was 7.6 (95% CI: 1.3–45.1), $p=0.025$. Because the incidence of thromboembolic events before adalimumab treatment (7.4/1,000 person-years) was close to that observed in ATA-negative adalimumab-treated patients, the authors suggest that the observed result was not due to systemic inflammation associated with rheumatoid arthritis. A subsequent report suggested that thromboembolic events associated with anti-TNF therapy is more likely due to TNF inhibition and the predisposition of some patients to lupus-like reactions, including antiphospholipid syndrome. (10) All 3 patients described by Korswagen had antibodies to double-stranded DNA (dsDNA), phospholipids, and/or β_2 -glycoprotein.

This same cohort was assessed for development of ATA and the clinical relevance of ATA during 3 years of follow-up. (11) After 3 years of adalimumab treatment, ATA were detected by RIA in 28% of patients ($n=76$). ATA titers correlated with adalimumab serum levels (measured by ELISA). In comparison with ATA-negative patients ($n=196$), ATA-positive patients were more likely to discontinue participation in the study due to treatment failure (38% vs. 14%, HR: 3.0 [95% CI: 1.6-5.5], $p<0.001$). ATA-negative patients were more likely than ATA-positive patients to:

- Have sustained minimal disease activity score in 28 joints (DAS28 <3.2 ; 48% vs. 13%; HR 3.6 [95% CI: 1.8-7.2; $p<0.001$).
- Achieve sustained remission (DAS28 <2.6 ; 34% vs. 4%; HR 7.1 [95% CI: 2.1-23.4], $p<0.001$).

Measurement of antibodies to infliximab or adalimumab

Garces et al. conducted a meta-analysis of studies of infliximab and adalimumab used to treat rheumatoid arthritis, ankylosing spondylitis, spondyloarthritis, psoriasis, Crohn's disease, and ulcerative colitis. (12) Databases were searched to August 2012, and 12 prospective cohort studies involving 860 patients (540 with rheumatoid arthritis, 132 with spondyloarthritis, 130 with IBD, and 58 with psoriasis) were included. The outcome of interest was drug response, assessed by using standard assessment scales for rheumatologic diseases (e.g., European League Against Rheumatism [EULAR] criteria for rheumatoid arthritis; Assessment in Ankylosing Spondylitis 20% response criteria or Ankylosing Spondylitis Disease Activity Score for spondyloarthritis; Psoriasis Area and Severity Index for psoriasis) and clinician assessment for IBD. Overall, detectable anti-drug antibodies were associated with a 68% reduction in drug response (pooled risk ratio [RR]: 0.32 [95% CI: 0.22–0.48]). Significant heterogeneity was introduced by varying use of immunosuppressant co-therapy (e.g., methotrexate) across studies. To assess anti-drug antibodies, most studies used RIA, which is less susceptible than ELISA to drug interference and may be more accurate.

Conclusions: Analytic validity of ATI testing was demonstrated using ELISA as a standard comparator. Test performance characteristics were considered robust. 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. Evidence for the clinical validity of ATI and ATA measurements suggests clinical correlations with infusion reactions and response to treatment. However, this evidence is mixed and limited in some

cases by flawed study designs. Heterogeneity in patient populations, use of concomitant immunosuppressants, methods and timing of antibody measurements, and outcome measures limits cross-study comparisons. One study (6) identified publication bias.

Clinical utility

Antibodies to infliximab

Inflammatory bowel disease (IBD)

Afif and colleagues 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. (13) 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. Seventy-two percent of the initial tests were ordered by a single physician. Clinical response to infliximab was retrospectively determined by the authors. 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. (13) 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. Since 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.

Steenholdt and colleagues attempted to establish clinically relevant threshold levels of infliximab and/or ATI. (14) A total of 106 patients with IBD (85 with Crohn's disease [CD] and 21 with ulcerative colitis [UC]) were identified over the course of 10 years (2001 to 2010). All patients were receiving infliximab treatment for IBD, as well as concurrent medications to prevent acute infusion reactions and to limit the development of ATI. Patients who received infliximab maintenance therapy were classified as having 1 of 2 responses: maintenance of response (patients had a good clinical response to infliximab induction therapy and continued this response over the course of maintenance treatment) or loss of response (patients who initially experienced a good clinical response to infliximab induction therapy but subsequently lost this response during maintenance treatment, resulting in discontinuation of therapy). The classification of infliximab response was based on clinical assessment; investigators were blinded to the results of the serum trough level analyses. Trough levels of infliximab and/or ATI were measured as the serum concentration immediately prior to an infusion of infliximab, using a radioimmunoassay.

Of the CD patients, 69% maintained their response to infliximab, and the remaining 31% had loss of response. Baseline characteristics of the 2 groups were well-balanced, and there were no significant differences in the total number of infliximab infusions administered to the 2 groups. Infliximab trough levels were significantly increased among CD patients who maintained response to therapy compared to patients who lost response ($p < 0.0001$). Using data from these patients, the authors assigned a cutoff value of 0.5 $\mu\text{g/mL}$ as clinically relevant for infliximab trough concentrations. Trough concentrations less than 0.5 $\mu\text{g/mL}$ were associated with a sensitivity of 86% (95% CI: 64-97) and a specificity of 85% (95% CI: 72-94) for identifying patients with a loss of response to infliximab maintenance therapy.

Trough levels of ATI were significantly higher in CD patients who had lost response to infliximab maintenance therapy compared to patients who had maintained response; $p < 0.001$). Using these data, the authors defined a cutoff value of 10 U/mL as clinically relevant for ATI concentrations. ATI trough levels of 10 U/mL or higher were associated with a sensitivity of 81% (95% CI: 61-93) and a specificity of 90% (95% CI: 79-96) for the identification of CD patients who had lost response to infliximab maintenance therapy. Similar determinations of infliximab and anti-infliximab antibody trough levels were made in the UC patients, although this group of patients was much smaller.

Limitations to this study included that it was retrospective and small, there was a lack of definitive criteria for response to infliximab maintenance therapy, and maintenance or loss of response was determined by chart review. Also, this study did not examine the changes in management made as a result of testing for ATI.

A commentary on the Steenholdt study (15) noted the limitations of the study and highlighted that the decision to continue or discontinue infliximab was based on clinical assessment by the gastroenterologist and not on infliximab trough level or ATI status, and that infliximab serum levels were measured as trough levels just prior to infliximab infusions but not at any other point in time. The commentary also stated that prospective studies should be required to base decision analyses on these cutoff levels and to see whether they support treatment algorithms to either increase infliximab dosage (low infliximab trough levels, no ATI), change to another anti-TNF monoclonal antibody (high ATI levels), or switch to another class of TNF inhibitors (adequate infliximab trough levels, no ATI).

Rheumatoid arthritis

Finckh and colleagues tested whether the presence of ATI and residual circulating infliximab levels prior to another infusion were associated with acquired infliximab resistance in rheumatoid arthritis (RA). (16) A multivariate logistic regression was used to analyze the relationship between ATI, residual infliximab concentrations, and acquired infliximab resistance in a nested cohort within a Swiss RA registry. Sixty-four RA patients on longstanding infliximab therapy were included; 24 had an acquired therapeutic resistance to infliximab, and 40 had continuous good response to infliximab. The 2 groups had similar disease characteristics, however, patients with acquired infliximab resistance required significantly higher dosages of infliximab and shorter infusion intervals than long-term good responders. The presence of residual infliximab tended to be associated with a decreased risk of acquired therapeutic resistance (odds ratio [OR]: 0.4, 95% CI: 0.1-1.5), while the presence of ATIs tended to be associated with an increased risk of acquired therapeutic resistance (OR: 1.8, 95% CI: 0.4 - 9.0). The presence of either high ATI levels or low residual infliximab concentrations was strongly associated with acquired therapeutic resistance to infliximab (OR: 5.9, 95% CI: 1.3 - 26.6). However, just 42% of patients with acquired infliximab resistance had either low infliximab or high ATI levels. The authors concluded that their results suggested that the assessment of ATIs and residual infliximab levels is of limited value for individual patients in routine clinical care.

Bendtzen and colleagues conducted a study to investigate whether serologic monitoring of infliximab bioavailability and immunogenicity in individual patients with RA would be useful to optimize treatment regimens to improve efficacy and tolerability. (17) Measurement of levels of anti-infliximab antibodies was by radioimmunoassay. Sera from 106 randomly selected RA patients were tested within 6 months of therapy initiation, and associations between findings of serum assays and disease activity, infusion reactions, and treatment failure occurring within 18 months were assessed. The trough serum infliximab levels after the first 2 intravenous infusions varied considerably between patients. At this stage, only 13% of the patients were anti-infliximab antibody-positive. With subsequent infusions, the frequency of antibody positivity rose to 30% and 44% (at 3 months and 6 months, respectively), accompanied by diminished trough levels of infliximab. Low infliximab levels at 1.5 months predicted antibody development and later treatment failure. There were highly significant correlations between high levels of antibodies and later dose increases, side effects, and cessation of therapy. Cotreatment with methotrexate resulted in slightly reduced antibody levels after 6 months; other disease-modifying antirheumatic drugs and prednisolone had no effect. The authors concluded that the development of anti-infliximab antibodies, heralded by low pre-infusion serum infliximab levels, was associated with

increased risk of infusion reaction and treatment failure and that early monitoring may help optimize dosing regimens for individual patients, diminish side effects, and prevent prolonged use of inadequate infliximab therapy.

Antibodies to adalimumab

Studies of the clinical utility of ATA measurement have not been published. Information about the Anser™ ADA test is provided by Prometheus on its website. Several posters presented at the annual Digestive Disease Week conference in May 2013 that address the clinical validity of the test are cited.

Conclusions: Evidence for the clinical utility of ATI and ATA testing currently is lacking. Uncontrolled retrospective studies in IBD demonstrate impacts of ATI testing on treatment decisions but cannot demonstrate improved patient outcomes compared to a no-testing strategy. Additional limitations of these studies include lack of clinical follow-up after treatment decisions were made (in Afif (13)) and the use of clinical assessments to guide treatment decisions (in Steenholdt (14)). Finally, determination of a clinically relevant threshold for ATI level is complicated by the use of various assay methods.

Summary

Antibodies-to-infliximab (ATI) or to adalimumab (ATA) are present in a substantial number of patients treated with infliximab or adalimumab, respectively, and there may be a correlation between the level of these antibodies and clinical response. However, the clinical utility of measuring antidrug antibody concentrations has not been established, as it is not known how patient management would change based on test results. Limited evidence describes changes in management after measurement of ATI, but does not compare these management changes to those made in the absence of ATI measurement. In addition, there are technical factors relating to the use of different assay methods across studies, it has not yet been established whether the use of threshold levels aids in the discrimination of treatment response, nor has the optimal timing of when to measure antibody levels been established.

Therefore, the measurement of antibodies to infliximab in a patient receiving treatment with infliximab is considered investigational, and the measurement of antibodies to adalimumab in a patient receiving treatment with adalimumab is considered investigational.

Practice Guidelines and Position Statements

Current clinical guidelines from the American College of Gastroenterology and the National Institute for Health and Care Excellence (NICE) do not recommend antidrug antibody testing for patients treated with TNF inhibitors.

Ongoing Clinical Trials

A search of online ClinicalTrials.gov database in August 2013 identified one relevant randomized controlled trial that is currently in progress, NCT00851565. The study is entitled, "Use of Combined Measurements of Serum Infliximab and Anti-infliximab Antibodies in the Treatment of Patients with Crohn's Disease Failing Infliximab Therapy." Adults with Crohn's disease who relapsed after a previous good response to infliximab are eligible. Target enrollment is 120 patients. In the intervention group, management of loss of response to infliximab will be guided by serum infliximab and ATI levels according to a prespecified algorithm. In the control group, loss of response will be managed according to current standards of care (i.e., to increase infliximab dose) without knowledge of serum infliximab or ATI levels. Primary outcome measures are the proportion of patients with response at week 12, defined by reduction in CD activity index, CDAI, for patients with luminal disease or by reduction in draining fistulas in patients with fistulizing disease (non-inferiority endpoint), and expenses related to Crohn's disease (superiority endpoint). The primary completion date (final data collection) was February 2012, and the study completion date is February 2014.

References

1. Ordas I, Mould DR, Feagan BG et al. Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. *Clin Pharmacol Ther* 2012; 91(4):635-46.

2. Kopylov U, Mazor Y, Yavzori M et al. Clinical utility of antihuman lambda chain-based enzyme-linked immunosorbent assay (ELISA) versus double antigen ELISA for the detection of anti-infliximab antibodies. *Inflamm Bowel Dis* 2012; 18(9):1628-33.
3. Wang SL, Ohrmund L, Hauenstein S et al. Development and validation of a homogeneous mobility shift assay for the measurement of infliximab and antibodies-to-infliximab levels in patient serum. *J Immunol Methods* 2012; 382(1-2):177-88.
4. Cassinotti A, Travis S. Incidence and clinical significance of immunogenicity to infliximab in Crohn's disease: a critical systematic review. *Inflamm Bowel Dis* 2009; 15(8):1264-75.
5. Lee LY, Sanderson JD, Irving PM. Anti-infliximab antibodies in inflammatory bowel disease: prevalence, infusion reactions, immunosuppression and response, a meta-analysis. *Eur J Gastroenterol Hepatol* 2012; 24(9):1078-85.
6. Nanda KS, Cheifetz AS, Moss AC. Impact of antibodies to infliximab on clinical outcomes and serum infliximab levels in patients with inflammatory bowel disease (IBD): a meta-analysis. *Am J Gastroenterol* 2013; 108(1):40-7; quiz 48.
7. Plasencia C, Pascual-Salcedo D, Nuno L et al. Influence of immunogenicity on the efficacy of longterm treatment of spondyloarthritis with infliximab. *Ann Rheum Dis* 2012; 71(12):1955-60.
8. Wang SL, Hauenstein S, Ohrmund L et al. Monitoring of adalimumab and antibodies-to-adalimumab levels in patient serum by the homogeneous mobility shift assay. *J Pharm Biomed Anal* 2013; 78-79:39-44.
9. Korswagen LA, Bartelds GM, Krieckaert CL et al. Venous and arterial thromboembolic events in adalimumab-treated patients with antiadalimumab antibodies: a case series and cohort study. *Arthritis Rheum* 2011; 63(4):877-83.
10. Masson PL. Thromboembolic events and anti-tumor necrosis factor therapies. *Int Immunopharmacol* 2012; 14(4):444-5.
11. Bartelds GM, Krieckaert CM, Nurmohamed MT et al. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. *JAMA* 2011; 305(14):1460-68.
12. Garces S, Demengeot J, Benito-Garcia E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. *Ann Rheum Dis* 2012.
13. Afif W, Loftus EV, Jr., Faubion WA et al. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. *Am J Gastroenterol* 2010; 105(5):1133-9.
14. Steenholdt C, Bendtzen K, Brynskov J et al. Cut-off levels and diagnostic accuracy of infliximab trough levels and anti-infliximab antibodies in Crohn's disease. *Scand J Gastroenterol* 2011; 46(3):310-8.
15. Dubeau MF, Ghosh S. Optimizing infliximab therapy for inflammatory bowel disease- the tools are getting sharper. *Gastroenterol Hepatol (N Y)* 2012; 8(2):134-6.
16. Finckh A, Dudler J, Wermelinger F et al. Influence of anti-infliximab antibodies and residual infliximab concentrations on the occurrence of acquired drug resistance to infliximab in rheumatoid arthritis patients. *Joint Bone Spine* 2010; 77(4):313-8.
17. Bendtzen K, Geborek P, Svenson M et al. Individualized monitoring of drug bioavailability and immunogenicity in rheumatoid arthritis patients treated with the tumor necrosis factor alpha inhibitor infliximab. *Arthritis Rheum* 2006; 54(12):3782-9.

Billing Coding/Physician Documentation Information

84999 Unlisted chemistry procedure

Additional Policy Key Words

N/A

Policy Implementation/Update Information

2/1/13 New policy; considered investigational.

12/1/13 Title changed to add "...and Adalimumab." "Measurement of antibodies to adalimumab in

a patient receiving adalimumab, either alone or as a combination test which includes the measurement of serum adalimumab levels” added to the policy statement; considered investigational.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.