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Medical Policy Manual

Topic: Measurement of Serum Antibodies to Infliximab and Adalimumab

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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

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 subcutaneousTNF 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 drug 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 treatment of 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.[2] For both drugs, antidrug antibodies have been associated with acute infusion reactions and delayed hypersensitivity reactions. 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. Studies evaluating the validation of the results between different assays are lacking, making inter-study comparisons difficult. The following assays have been studied:

- First-generation assays (i.e., enzyme-linked immunoabsorbent assays [ELISA]) have limited clinical utility because they can only measure antidrug antibodies in the absence of detectable drug levels due to interference of the drug with the assay.
- The radioimmunoassay (RIA) method is limited by the complexity of the test, prolonged incubation time, and safety concerns related to the handling of radioactive material.
- The homogenous mobility shift assay (HMSA) using high-performance liquid chromatography has the advantage of being able to measure antidrug antibodies when infliximab is present in the serum. However, inter-comparison studies which evaluate the validation of results between different assays are lacking.

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 ATIs and infliximab levels and utilize these assays to predict treatment response.[3] 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. offers non-radiolabeled fluid-phase HMSA tests called the Anser™IFX test for infliximab and Anser™ADA for adalimumab. Neither of these tests are ELISA-based and both can measure antidrug antibodies in the presence of detectable drug levels, improving upon a major limitation of the ELISA method. Both tests measure serum 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.

MEDICAL POLICY CRITERIA

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

SCIENTIFIC EVIDENCE

Validation of the clinical use of any diagnostic test focuses on 3 main principles:

- Technical performance for such testing may compare test measurements with a gold standard and may also compare results taken on different occasions (test-retest).

- Diagnostic performance (i.e., sensitivity, specificity, and positive and negative predictive value) is evaluated by the ability of a test to accurately predict the clinical outcome in appropriate populations of patients. The sensitivity of a test is the ability to detect a disease when the condition is present (true positive). The specificity is the ability to detect the absence of a disease or outcome when the disease is not present (true negative).

- 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.

Literature Appraisal

Most studies of antibodies to infliximab or adalimumab report on both serum drug levels, as well as levels of drug-antibodies, and correlate these levels to disease response rates. Except for studies regarding the feasibility of the combined test, serum drug levels and disease response are not the focus of 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.

Technical Feasibility

Measurement of Antibodies to Infliximab

The technical performance must be compared to the established gold standard for measuring the development of antidrug antibodies. This is particularly problematic, since there is currently no gold standard as developed methods for measuring ATIs, such as the ELISA and RIA methods, are no longer available and/or contain significant limitations.

- In 2012, 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.[4] 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.

- In 2012, Kopylou and colleagues analyzed test results from 63 serum samples, comparing a double-agent (DA) ELISA testing method to an alternative antihuman lambda chain (AHLC) antibody ELISA test.[5] All samples were tested using both testing methods and 22/63 and ATIs were demonstrated in 22/63 (34.9%) and 18/63 (28.5%) of patients by AHLC and DA assay, respectively ($P = 0.6$). Lower serum infliximab and ATIs were detected in four patients by the AHLC method but not the DA method, supporting the theory that DA ELISA testing is ineffective when any treatment is present, limiting the times when this type of testing can be performed.

- Also in 2012, Vande Casteele and colleagues compared three (A, B, C) different European assays using both serum and spiked control samples of 62 inflammatory bowel patients.[6] Authors concluded that all ATI assays showed good linear correlation (Pearson $r = 0.91$ for A vs. B, 0.83 for A vs. C and 0.73 for B vs. C). However, one assay detected false positive infliximab levels in nearly a fifth of the samples.

Conclusion

To date ELISA is the most commonly studied ATI testing assay for the detection of anti-infliximab antibodies, although a large variety of assay tests are available. However, drug interference limits the reliability of the ELISA test and it is no longer available from the manufacturer, having been replaced by the Anser IFX™ test. There are no peer reviewed publications regarding the Anser IFX™ test. No other ATI assay has been validated as the new gold standard for detecting antibodies to infliximab treatment. Therefore, conclusions reached in subsequent studies analyzed within this policy must be considered within this context.

Measurement of Antibodies to Adalimumab

In 2013, Wang and colleagues developed and validated a non-radiolabeled HMSA to measure antibodies-to-adalimumab (ATA) and adalimumab levels in serum samples.[7] 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. Without a comparison to an alternative method of antibody detection, the analytic validity of the ATA test remains uncertain.

Diagnostic Performance

Measurement of Antibodies to Infliximab

Inflammatory Bowel Disease

- Steenholdt and colleagues attempted to establish clinically relevant threshold levels of infliximab and/or ATI.[8] 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 µg/mL as clinically relevant for infliximab trough concentrations. Trough concentrations less than 0.5 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; $p<.0001$). 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[9] 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

No studies were found which analyzed the diagnostic performance of ATI assay tests in patients with RA, undergoing infliximab treatment.

Measurement of Antibodies to Adalimumab

In the 2013 Wang study noted above, 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%.[7] The calculated cut point for serum adalimumab levels was 0.68 µg/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 µg/mL), 68% were ATA positive; in samples with adalimumab levels >20 µg/mL, 18% were ATA positive.

Conclusion

The evidence regarding the diagnostic performance of ATI testing in patients with inflammatory bowel disease is limited to a small study which recommended ATI trough cutoff values for identifying patients with CD and UC who will become treatment resistant. Cut points were also suggested in a recent study of adalimumab and ATA in patients who were losing response to adalimumab treatment. However these cut-offs were not used to alter patient treatment decisions, thus were not validated. No studies evaluated the performance of ATI or ATA testing, using specified cut-points, to identify patients who will develop resistance to infliximab or adalimumab treatment.

Clinical Utility

Measurement of Antibodies to Infliximab

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.[10] The authors concluded that there was no clear evidence regarding the safety or efficacy of ATI development and

therefore, not need to measure or prevent them in patients undergoing infliximab treatment. In addition, the authors concluded:

- The biological and clinical mechanisms of ATI development are poorly understood,
- The incidence of ATI in vivo depends on multiple analytical and clinical factors (both patient- and treatment-related),
- The presence of ATI is weakly and variably associated with clinical response and infusion reactions (but not with reactions relevant to clinical decision making),
- Enormous variation in the methods of reporting ATI and immunogenicity of infliximab make almost any comparison between studies (few with clinical relevance) impossible.

Inflammatory Bowel Disease

- 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.[11] 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 ($P<0.00001$). 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 ATI are at an increased risk of infusion reactions, but have similar rates of remission compared with patients who test negative for ATI.

- Nanda and colleagues conducted a meta-analysis that reported on clinical outcomes according to the presence or absence of ATI in patients with inflammatory bowel disease (IBD).[12] 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.

- A meta-analysis by Plasencia and colleagues evaluated outcomes of patients treated with infliximab for spondyloarthritis, psoriatic arthritis and IBD.[13] Over a mean follow-up of 7 years, an ELISA-based tests was used to monitor for ATI development. Similar to the Nanda study, outcomes were limited due to the ATI testing method and that serum samples were collected from patients after treatment began which is known limit the reliability of ELISA test results.

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).[14] 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 ATI 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.[15] 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. Similar to other studies[16], 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. Co-treatment 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.

- In 2013, Krintel and colleagues also investigated the association of ATI with adverse drug reaction or resistance in RA patients receiving infliximab.[16] All 218 patients were identified through the DANBIO registry, however during the 52 week follow-up period, a third of patients withdrew from the study due to adverse events or treatment failure. Antibodies were detected in over half (n = 118) of the initial study population and a significant increased risk of adverse drug reactions was observed in patients who had developed antibodies after 6 and 14 week follow-up, compared to those who were without antibodies [hazard ratio (HR) = 5.06, 95% CI 2.36, 10.84; P < 0.0001]. Overall, the authors concluded that patients with early ATI development were less likely to achieve sustained remission; however, these results are limited by the high percentage of patients who withdrew, precluding any conclusions as to the association of ATI with disease remission or adverse drug reaction.

- Similarly, Hoshino and colleagues found an association between ATI and lower infliximab levels and concluded that ATI were significantly higher in the non-responder group.[17] However, these association studies do not establish how accurately ATI test measurements predict treatment resistance in patients with RA.

- van der Maas and colleagues reported on 147 RA patients treated with infliximab for at least 6 months and found that low and high infliximab trough levels were observed in RA patients with low disease activity.[18] In addition, anti-infliximab antibodies were also found in one-third of stable patients, suggesting that the presence of ATI and low infliximab levels are not always an indicator of future treatment resistance. Further study, with large, randomized controlled trials, evaluating remission and infliximab treatment resistance rates of RA patients with and without ATI are needed.

Additional studies[19,20] were identified which evaluated the association of ATI and response to treatment and infusion reactions; however, these studies did not evaluate the clinical utility of these test results. Well-designed randomized trials are needed, which demonstrate how antibody test results are used to guide treatment decisions and improve health outcomes compared to patients treated without these results.

Other Indications

A 2014 systematic review by Hsu et al. evaluated the prevalence of antidrug antibodies against infliximab, etanercept, adalimumab, and ustekinumab in patients with psoriasis[21] using a pooled analysis of 25 studies. The study observed an association between the development of antidrug antibodies and diminished treatment response between trough levels and ATI; however, further study will be required in order to establish the implications this association will have on treatment decisions for patients with psoriasis.

Additional studies[22] were identified which evaluated the association of antidrug antibodies and response to treatment and infusion reactions; however, the clinical utility of these test results has yet to be evaluated.

<u>Measurement of Antibodies to Adalimumab</u>

Inflammatory Bowel Disease

In 2014, Imaeda and colleagues evaluated low serum adalimumab trough levels and loss of clinical response to adalimumab in 40 patients with Crohn's disease (CD).[23] The presence of ATA was

statistically significantly higher in patients who lost response to adalimumab; however, this study did not demonstrate how treatment decisions were altered as a result of ATA testing.

Rheumatoid Arthritis

Bartelds and colleagues retrospectively assessed 272 consecutive patients with rheumatoid arthritis treated with adalimumab for development of ATA and the clinical relevance of ATA during 3 years of follow-up.[24] After 3 years of adalimumab treatment, ATA were detected by radioimmunoassay (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).

Additional studies[19,20] were identified which evaluated the association of ATA and response to treatment and infusion reactions; however, these studies did not evaluate the clinical utility of these test results. Well-designed randomized trials are needed, which demonstrate how antibody test results are used to guide treatment decisions and improve health outcomes compared to patients treated without these results.

Other Indications

As noted above, while there have been association studies in[21,22] other conditions such as psoriasis and spondyloarthritis, the clinical utility of measurement of antidrug antibodies has not been reported.

Conclusion

The value of using ATI or ATA testing as a means of predicting treatment resistance is unknown. Studies which investigate the use of this test to alter patient treatment decisions are few and those which do, lack comparison with treatment decisions made in the absence of test information. The majority of studies investigated the use of antibody tests are mainly association studies which do not demonstrate how patient management is impacted with information from test results. Large, well-designed trials which compare patient treatment decisions between test and control groups are necessary to validate the utility of antibody testing to improve patient outcomes.

Clinical Practice Guidelines

There are no clinical practice guidelines which recommend the use of anti-infliximab antibody or anti-adalimumab antibody testing for any indication.

Summary

Antibodies to infliximab (ATI) or to adalimumab (ATA) 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. However, current evidence is insufficient to determine whether measurement of these antidrug antibodies can be used in patient management to improve health outcomes. In addition, the

optimal timing of when to measure antibody levels has not been established. Therefore, the measurement of antidrug antibodies in patients receiving treatment with infliximab or adalimumab is considered investigational.

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CROSS REFERENCES

None

CODES	NUMBER	DESCRIPTION
CPT	84999	Unlisted chemistry procedure
HCPCS	None	