Medical Policy

BlueCross BlueShield of Kansas
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Title: Measurement of Serum Antibodies to Infliximab

Professional
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DESCRIPTION

Infliximab (Remicade® Centocor) is a 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. Secondary loss of response to infliximab is seen in a certain percentage of patients; the development of anti-infliximab antibodies has been suggested as one reason for nonresponse.

Background

Infliximab in autoimmune disease

Infliximab is a chimeric (mouse/human) anti-tumor necrosis factor (TNF)-alpha monoclonal antibody. Therapy with monoclonal antibodies like infliximab 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) Antibodies to infliximab have also been associated with acute infusion reactions and delayed hypersensitivity to infliximab.

Detection of antidrug antibodies

The detection and quantitative measurement of anti-infliximab antibodies, also referred to as human antichimeric antibodies (HACA) or antibodies to infliximab (ATI), has been fraught with difficulty. First-generation assays, (i.e., enzyme-linked immunoabsorbant 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.

Treatment options for patients with secondary loss of response to infliximab

A diminished or suboptimal response to infliximab 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 an ELISA-based test for the measurement of serum infliximab and human antichimeric antibodies (HACA). This test is set to be discontinued in August 2012 and replaced with an HMSA called the Anser™IFX test. The Anser IFX test is not ELISA-based and can measure antibodies to infliximab in the presence of serum infliximab, improving upon a major limitation of the ELISA method. Anser IFX is offered as a combined test measuring serum concentrations of infliximab and antibodies to infliximab.

This test was developed and its performance characteristics determined by Prometheus Laboratories Inc. It has not 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.

POLICY

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 **experimental / investigational**.

RATIONALE

Literature Review

This policy is based on a search of the MEDLINE database through July 2012. Literature that describes the analytic validity, clinical validity, and clinical utility of measuring serum antibodies to infliximab was sought. Most studies of antibodies to infliximab report on both serum infliximab levels, as well as levels of antibodies to infliximab, and correlate these levels to response rates of disease. Serum infliximab levels and disease response will not be addressed in this policy and therefore the data reported on antibodies to infliximab will be highlighted from the aforementioned studies. Most of the data on the use of measurements of antibodies to infliximab are from patients with inflammatory bowel disease, with limited literature for other diseases such as rheumatoid arthritis.

Analytic and clinical validation of measurements 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. (2) 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. The false positive rate with this cut point was 3%.

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. (3) 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 interpretation possible from different studies (few with clinical relevance). 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. (4) 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 ATIs are at an increased risk of infusion reactions, but have similar rates of remission compared with patients who test negative for ATIs.

Clinical utility of antibodies to infliximab

Inflammatory bowel disease

Afif and colleagues evaluated the clinical utility of measuring ATI (referred to as HACA in the study) and infliximab concentrations by retrospectively reviewing the medical records of patients with inflammatory bowel disease (IBD) who had had ATI and infliximab concentrations measured. The study sought to determine whether these results affected clinical management. (5) 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. (5) Limitations to the study included its retrospective design and that the testing for antibodies to infliximab was performed using the enzyme-linked immunoabsorbant assays (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. (6) 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 (7) 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). (8) 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. (9) 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.

Summary
Antibodies to infliximab (ATI) are present in a substantial number of patients treated with infliximab, and there may be a correlation between the level of these antibodies and clinical response. However, the clinical utility of measuring anti-infliximab 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 response to infliximab, 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.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

84999 Unlisted chemistry procedure

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

DIAGNOSES

Experimental / investigational for all diagnoses related to this policy.

REVISIONS

06-07-2013	Policy added to the bcbsks.com web site.
	Effective for Institutional providers 30 days after the Revision Date, 07-08-2013.

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