Description of Procedure or Service

Policy Description
Targeted inhibitors of tumor necrosis factor-alpha (TNF) (including infliximab, adalimumab, etanercept, golimumab, etc.) are widely used in the treatment of a number of inflammatory conditions, including rheumatoid arthritis (RA), spondyloarthritis, inflammatory bowel disease, and psoriasis (Bendtzen, 2017a).

Immunopharmacologic monitoring of circulating drug and anti-drug antibody levels has been proposed to manage loss of response due to the development of anti-drug antibodies, which may promote adverse effects and diminish drug efficacy (Bendtzen, 2017a; Tighe & McNamara, 2017).

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

Immunopharmacologic monitoring of Infliximab, Adalimumab and other therapeutic serum antibodies is not covered for any indication.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When immunopharmacologic monitoring of therapeutic serum antibodies is covered

Not applicable.

When immunopharmacologic monitoring of therapeutic serum antibodies is not covered

The measurement of the serum drug levels and/or measurement of the antibodies to the following drugs, either alone or in a combination test, in an outpatient setting are investigational:

a. adalimumab
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b. infliximab
c. infliximab-dyyb
d. infliximab-abda
e. vedolizumab

Reimbursement is not allowed for the measurement of the serum drug levels and/or measurement of the antibodies to the following drugs, either alone or as a combination test, in an outpatient setting:

a. certolizumab
b. etanercept
c. golimumab
d. rituximab
e. ustekinumab

Policy Guidelines

**Background**

TNF inhibitors competitively inhibit the binding of TNF to its receptors to reduce inflammation and stop disease progression (Lis, Kuzawińska, & Bałkowiec-Iskra, 2014). They are used for treatment of inflammatory conditions such as rheumatoid arthritis (RA), psoriatic arthritis, juvenile arthritis, inflammatory bowel disease (Crohn’s and ulcerative colitis), ankylosing spondylitis (Bendtzen, 2017b; Lis et al., 2014).

Some patients do not respond to TNF inhibitors, while others achieve an initial response to induction therapy but lose this response over time with maintenance treatment. The reason for this is unknown. Steenholdt, et al. (2012) states, “the reasons for these therapeutic failures remain a matter of debate. One possibility is that loss of response is due to an immunologic mechanism, whereby the patient mounts an immune response to infliximab, thus forming anti-infliximab antibodies. Multiple studies in CD patients have linked the development of anti-infliximab antibodies with loss of treatment response and shorter duration of response. Another possibility is that loss of response to infliximab is pharmacologic in nature; under this mechanism, individuals' differing pharmacokinetic or pharmacodynamic profiles may contribute to their inability to maintain a therapeutic serum level of infliximab. Indeed, low serum infliximab concentrations have been linked to a lack of clinical response in both CD and UC based on clinical trial data showing robust efficacy in these conditions.”

**Clinical Validity and Utility**

Wang et al. (2012) developed and validated a non-radiolabeled homogeneous mobility shift assay (HMSA) to measure the antibodies-to-infliximab (ATA) and infliximab levels in serum samples. Full method validation was performed on both the ATA- 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 interassay precision rates (as indicated by the coefficient of variation [CV]) for the ATA- and infliximab-HMSA were less than 4 percent and less than 15 percent, respectively, and less than 6 percent and less than 15 percent, respectively, considered to be robust.

Wang et al. (2013) developed and validated a nonradiolabeled HMSA to measure antibodies-to-adalimumab (ATA) and adalimumab levels in serum samples. Analytic validation of performance characteristics (calibration standards, assay limits, intra- and inter-assay precision, linearity of dilution, substance interference) was performed for both the ATA- and adalimumab-HMSA. Because the elimination half-life of adalimumab (10-20 days) overlaps the dosing interval (every 2 weeks), 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 CV) was <20 percent and <3 percent, respectively; interassay (run-to-run, analyst-to-analyst and instrument-to-instrument) precision and accuracy were less than 12 percent and less than 22 percent, respectively. For the ATA-HMSA, CVs for intra-assay precision and accuracy were less than 3 percent and less than 13 percent, respectively; CVs for interassay precision and accuracy were less than 9 percent and less than 18 percent, respectively. ELISA could not be used as a standard comparator due to competition from circulating drug.

Van stappen et al (2016) validated a rapid, lateral flow-based assay (LFA) for quantitative determination of infliximab and to assess thresholds associated with mucosal healing in patients with ulcerative colitis. They found that “The LFA showed an excellent agreement with enzyme-linked immunosorbent assay (ELISA) for quantification of infliximab, as observed from Pearson and intraclass correlation coefficients of 0.95 and 0.95 during induction and 0.93 and 0.87 during maintenance therapy, respectively. In total, 45% of patients achieved MH. Using the LFA, week 14 TC ≥2.1 μg/ml (AUROC: 0.819, P=0.008) were associated with MH. After 2 years follow-up, 77% of patients with MH were still receiving infliximab therapy vs. 25% of patients without MH.” They concluded that “With a time-to-result of 20 min, individual sample analysis and user-friendliness, the LFA outplays ELISA as a rapid, accurate tool to monitor infliximab concentrations.”

Steenholdt et al (2014) “investigated the cost-effectiveness of interventions defined by an algorithm designed to identify specific reasons for therapeutic failure.” They found that “Costs for intention-to-treat patients were substantially lower (34%) for those treated in accordance with the algorithm than by IFX dose intensification: € 6038 vs € 9178, p<0.001. However, disease control, as judged by response rates, was similar: 58% and 53%, respectively, p=0.81; difference 5% (-19% to 28%).” They concluded that “treatment of secondary IFX failure using an algorithm based on combined IFX and IFX antibody measurements significantly reduces average treatment costs per patient compared with routine IFX dose escalation and without any apparent negative effect on clinical efficacy.”

Roblin et al (2014) conducted a prospective study with 82 patients with inflammatory bowel disease (IBD) having a disease flare while being on ADA 40 mg every 2 weeks. All patients were primary responders to ADA therapy and were anti-tumor necrosis factor (TNF) naive. ADA trough levels and antibodies against ADA (AAA) were measured. All patients were optimized with ADA 40 mg weekly. Four months later, in the absence of clinical remission, patients were treated with infliximab. The researchers concluded that “the presence of low ADA trough levels without AAA is strongly predictive of clinical response in 67% of cases after ADA optimization. Conversely, low ADA levels with detectable AAA are associated with ADA failure, and switching to IFX should be considered. ADA trough levels >4.9 μg/ml are associated with failure of two anti-TNF agents (ADA and IFX) in 90% of cases and switching to another drug class should be considered.”

Mitchel et al (2016) studied if infliximab (IFX) therapeutic drug monitoring (TDM) allows for objective decision making in patients with inflammatory bowel disease (IBD) and loss of response. They found that “A trend towards increased remission rates was associated with appropriate changes in management following TDM results. Many patients with therapeutic IFX concentrations did not undergo an appropriate change in management, potentially reflecting a lack of available out-of-class options at the time of TDM or due to uncertainty of the meaning of the reported therapeutic range.”

Barlow et al (Barlow, Mohammed, & Berg, 2016) studied “the clinical utility of antibodies as an adjunct to trough infliximab.” They concluded that “The relationship between trough infliximab and C-reactive protein differed depending on antibody status and there was no association.
between C-reactive protein and the presence or absence of antibodies. Our findings support measurement of anti-infliximab antibodies only in the context of low infliximab concentrations <1 µg/mL. A higher therapeutic cut-off may be relevant in patients with negative antibodies. Further work is indicated to investigate the clinical significance of positive antibodies with therapeutic infliximab concentrations.”

Moore et al (2016) performed a systematic review and meta-analysis of studies that reported serum infliximab levels according to outcomes in IBD. They found that “A total of 22 studies met the inclusion criteria, including 3483 patients; 12 studies reported IFX levels in a manner suitable for determining effect estimates. During maintenance therapy, patients in clinical remission had significantly higher mean trough IFX levels than patients not in remission: 3.1 µg/ml versus 0.9 µg/ml. The standardised mean difference in serum IFX levels between groups was 0.6 µg/ml (95% confidence interval [CI] 0.4-0.9, p = 0.0002). Patients with an IFX level > 2 µg/ml were more likely to be in clinical remission (risk ratio [RR] 2.9, 95% CI 1.8-4.7, p < 0.001), or achieve endoscopic remission [RR 3, 95% CI 1.4-6.5, p = 0.004] than patients with levels < 2 µg/ml.” The study concluded that “There is a significant difference between serum infliximab levels in patients with IBD in remission, compared with those who relapse. A trough threshold during maintenance > 2 µg/ml is associated with a greater probability of clinical remission and mucosal healing.”

Tighe and McNamara (2017) reviewed the role of immunomonitoring in helping to achieve long lasting deep remission and mucosal healing. They concluded that “Immunomonitoring is helping us to understand the pharmacokinetics behind anti-TNFα therapies, and also how best to optimise management of IBD. Tailoring treatment to the individual in a treat to target fashion, offers the hope of improving response and remission rates, as well as achieving mucosal healing. This needs to be verified, using randomised clinical trials, comparing with the current standard approach. Going forward, we need to understand further the significance of immunogenicity, the impact of anti-TNFα antibody formation, and there is a strong need for greater availability, of more affordable and rapid turnaround ELISA or alternative techniques, to fully implement the potential of immunomonitoring.”

State and Federal Regulations, as applicable
This test is considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories.
LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA’88).
As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

Practice Guidelines and Position Statements
National Institute for Health and Clinical Excellence (NICE)
The 2016 Guidelines for Therapeutic monitoring of TNF-alpha inhibitors in Crohn’s disease (NICE, 2016) stated that “enzyme-linked immunosorbent assay (ELISA) kits show promise for therapeutic monitoring of tumor necrosis factor (TNF)-alpha inhibitors in people with Crohn's disease but there is insufficient evidence to recommend their routine adoption”.

American College of Gastroenterology
The ACG published guidelines (Feuerstein, Nguyen, Kupfer, Falck-Ytter, & Singh, 2017) on Therapeutic Drug Monitoring in Inflammatory Bowel Disease recommending:
In adults with active IBD treated with anti-TNF agents, the AGA suggests reactive therapeutic drug monitoring to guide treatment changes. Conditional recommendation, very low quality of evidence.
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In adult patients with quiescent IBD treated with anti-TNF agents, the AGA makes no recommendation regarding the use of routine proactive therapeutic drug monitoring.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 84999, 80145, 80230, 80235, 80280, 80285, 80299

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


NICE. (2016). Therapeutic monitoring of TNF-alpha inhibitors in Crohn’s disease (LISA-TRACKER ELISA kits, IDKmonitor ELISA kits, and Promonitor ELISA kits) | Guidance and
An Independent Licensee of the Blue Cross and Blue Shield Association

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guidelines | NICE. from NICE https://www.nice.org.uk/guidance/dg22/chapter/1-Recommendations


Specialty Matched Consultant Advisory Panel review 2/2020

Policy Implementation/Update Information

1/1/19 New policy developed. Immunopharmacologic Monitoring of Infliximab, Adalimumab and other Therapeutic Serum Antibodies is considered investigational. BCBSNC does not provide coverage for investigational services or procedures. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (an)

10/1/19 Policy statement revised to read: Reimbursement is not allowed for immunopharmacologic monitoring of Infliximab, Adalimumab and other therapeutic serum antibodies. Wording revised in the Not Covered section. “Investigational” changed to read “Reimbursement is not allowed…”. Deleted coding grid. Notification given 10/1/2019 for effective date 12/2/2019. (an)

12/10/19 Policy title changed from “Immunopharmacologic Monitoring of Infliximab, Adalimumab and other Therapeutic Serum Antibodies” to “Immunopharmacologic Monitoring of Therapeutic Serum Antibodies”. Avalon Q3 CAB Update. Coding section updated to reflect new codes for 2020. When not covered section reworded for clarity to include both serum antibodies or serum drug levels either alone or in combination with listed drugs. (eel)
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12/31/19  Entry date on previous update note corrected from 10/1/19 to 12/10/19. (eel)

3/10/20  Specialty Matched Consultant Advisory Panel review 2/19/2020. No change to policy statement. (eel)

5/26/20  Language under When not covered section updated from reimbursement to investigational for adalimumab, infliximab, infliximab-dyyb, infliximab-abda, and vedolizumab. Policy statement clarified as “Immunopharmacologic monitoring of Infliximab, Adalimumab and other therapeutic serum antibodies is not covered for any indication.”  80299 added to Coding section. (eel)

6/9/20  Clarified language in change log entry dated 5/26/20.  80187 removed from Coding section. (eel)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.