HEALTH PLANS
UNIVERSITY OF UTAH

Medical Policy

Drug Levels and Antibody Testing for Infliximab, Adalimumab, Vedolizumab and Ustekinumab

Policy MP-026

Origination Date: 07/15/2021

Reviewed/Revised Date: 06/21/2023

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Current Effective Date: 06/21/2023

Disclaimer:

1. Policies are subject to change in accordance with State and Federal notice requirements.
2. Policies outline coverage determinations for U of U Health Plans Commercial and Healthy U (Medicaid) plans. Refer to the "Policy" section for more information.
3. Services requiring prior-authorization may not be covered, if prior-authorization is not obtained.
4. This Medical Policy does not guarantee coverage or payment of the service. The service must be a benefit in the member's plan and the member must be eligible for coverage at the time of service. Additional payment guidelines may be applied that are not included in this policy.

Description:

Infliximab, adalimumab, ustekinumab, and vedolizumab are monoclonal antibody drugs used to treat inflammatory conditions, such as rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis; inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis), ankylosing spondylitis, and plaque psoriasis. These biological agents are generally given to patients who fail conventional medical therapy, and are typically effective for the induction and maintenance of clinical remission. However, during use, some patients develop anti-drug antibodies (ADAs) that neutralize the anti-inflammatory action of these drugs. This response may diminish the potential long-term efficacy of these drugs.

The reasons for therapeutic failures remain a matter of debate but include accelerated drug clearance (pharmacokinetics) and neutralizing agent activity (pharmacodynamics) due to the development of ADAs. Another proposed mechanism to determine a patient's loss of response to the monoclonal antibody drugs is therapeutic drug monitoring (TDM). These blood tests are used to measure and monitor both the serum drug level and antibody level to these drugs. However, the detection and quantitative measurement of ADAs are difficult because of drug interference and identifying when antibodies have a neutralizing effect. Which leaves several obstacles to their regular use, including when to use TDM, how to accurately interpret and apply the results of such testing, and defining the optimal drug concentration thresholds and ranges to target.

Policy Statement and Criteria

1. Commercial Plans

U of U Health Plans does not cover testing for the measurement of antibodies and/or serum drug levels to monoclonal antibody (MAB) drugs, including anti-tumor necrosis factor (TNF) drugs, either alone or as a combination test, as it is considered investigational or unproven.

U of U Health Plans does NOT cover the following tests (may not be an all-inclusive list):

- Anser® ADA
- Anser® IFX
- Anser® VDZ
- Anser® UST
- Miraca Life Sciences' InformTx™
- DoseASSURE™-LabCorp
- LabCorp®-ECLIA

2. Medicaid Plans

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website at: https://medicaid.utah.gov/utah-medicaid-official-publications/ or the Utah Medicaid code Look-Up tool

CPT/HCPCS codes covered by Utah State Medicaid may still require further evaluation to determine medical necessity for coverage.

Clinical Rationale

In 2016, the National Institute for Health and Clinical Excellence (NICE) (NICE, 2016; Singh et al., 2019) issued guidance on therapeutic monitoring of tumor necrosis factor (TNF)-alpha inhibitors in the treatment of patients with Crohn's disease. NICE stated that "enzyme-linked immunosorbent assay (ELISA) kits show promise for therapeutic monitoring of -alpha inhibitors in people with Crohn's disease but there is insufficient evidence to recommend their routine adoption" and recommended that laboratories monitoring (TNF)-alpha inhibitors in patients with Crohn disease who have lost response to the treatment should "work with clinicians to collect data through a prospective study, for local audit, or for submission to an existing registry." NICE also stated that "Enzyme-linked immunosorbent assay (ELISA) tests for therapeutic monitoring of tumor necrosis factor (TNF)-alpha inhibitors (drug serum levels and antidrug antibodies) show promise but there is currently insufficient evidence to recommend their routine adoption in rheumatoid arthritis."

In 2017, Feuerstein et al. published the American College of Gastroenterology Institute guidelines on therapeutic drug monitoring in inflammatory bowel disease. The guidelines note that "When anti-drug antibodies are detected, it is unclear what antibody level is clinically meaningful…. The reporting of anti-drug antibodies is variable between commercial assays, with some assays being very sensitive for detecting very-low-titer antibodies of limited clinical significance. Uniform thresholds for clinically

relevant antibody titers are lacking. At this time, it is unclear how antibodies affect drug efficacy when both active drug and antibodies are detected. In cases of low trough concentrations and low or high anti-drug antibodies, the evidence to clarify optimal management is lacking." These guidelines did not address therapeutic drug monitoring in patients treated with vedolizumab or ustekinumab, due to a scarcity of data at the time of publication.

A 2018 retrospective, multicenter study (Papamichael et. al.) reviewed drug retention in inflammatory bowel disease (IBD) patients of whom infliximab was optimized to overcome immunogenicity and variables associated with drug retention. This study consisted of consecutive IBD patients with antibodies to infliximab (ATI), based on either proactive or reactive therapeutic drug monitoring, who underwent infliximab optimization (increasing dose, shortening interval, adding an immunomodulator, or combination) to overcome immunogenicity from September 2012 to July 2015; they were followed through December 2015. ATI were analyzed using the drug-tolerant Prometheus homogeneous mobility shift assay. Drug retention was defined as no need for drug discontinuation due to secondary loss of response (SLR) or serious adverse event. The cohort consisted of 22 patients (Crohn's disease, n = 15). At the end of follow-up [median, (IQR): 17.3 (10.5-32.8) months] 77% (15/22) of patients were still on drug. Univariable Cox proportional hazards regression analysis identified first detectable ATI titer as the only variable associated with drug retention (HR: 0.89; 95% CI: 0.82-0.98, p = 0.016). Receiver-operating characteristic analysis identified an ATI titer < 8.8 U/mL associated with drug retention. The authors concluded that in real-life clinical practice, optimization of infliximab therapy can prevent drug discontinuation in approximately 3/4 of patients with ATI, especially in those with low titers. However, large prospective studies are needed to confirm these data.

A 2019 small cohort study (Van den Berghe et. al.) evaluated ADA to vedolizumab in 40 patients with IBD. This study included the development of an ELISA-based test to measure ADA in the presence of the drug. Anti-vedolizumab antibodies and vedolizumab trough levels were measured after six weeks of treatment and after treatment discontinuation. At the six-week follow-up, three (8%) of the patients were positive for ADA, but this appeared to be transient. None of the patients who discontinued vedolizumab were positive for ADA at the time of their last infusion or after discontinuation. It did not appear that immunogenicity played a major role in vedolizumab treatment failure.

A 2019 clinical utility study (Papamichael et. al.) examined current data regarding therapeutic drug monitoring (TDM) for biologic therapies in IBD. Biologic Therapies include anti-tumor necrosis factor (anti-TNF) agent's infliximab and adalimumab. Up to one-third of patients with Crohn's disease (CD) and ulcerative colitis (UC) show primary non-response (PNR) to biologic therapies, and up to 50% of patients after an initial clinical response stop therapy for either SLR- or a serious adverse event. Both PNR and SLR are due to either pharmacokinetic (PK) or pharmacodynamic (PD) problems. PK issues are associated with inadequate drug exposure, often because of the development of antidrug antibodies (ADA), whereas PD issues are typically related to inflammatory process unrelated to the targeted immunoinflammatory pathway. TDM, defined as the assessment of drug concentrations and ADA, is an important tool for optimizing biologic therapy. However, there are still some limitations when applying TDM into clinical practice, such as when to use TDM, proper interpretation and application of the results, and the identification of the optimal window/ thresholds to target. These therapeutic windows or thresholds appear to vary on the basis of the outcome of interest and the IBD phenotype. Most of the data on implementation of TDM refer to anti-TNF therapies and the maintenance phase of treatment. The authors concluded that although well-designed large prospective studies are lacking, there are preliminary data mainly from retrospective studies that demonstrate that proactive TDM is associated with better therapeutic outcomes compared with empiric dose optimization and/or reactive TDM. However, major limitations of the evidence relate to the lack of large prospective studies and RCTs on

TDM of biologic therapy applied on different IBD phenotypes and sparse data on induction therapy and on biologic agents other than infliximab and adalimumab. Also, it is unclear whether trough concentrations are the best predictor of initial response to biologics, compared with peak drug concentrations or total drug exposure. Further RCTs to establish the utility of proactive TDM, particularly during the induction phase, should be performed. Along with future directions focusing on the development of accurate, easily accessible, and affordable rapid assays, dashboards to allow fast dosing adaptation and incorporation of predictive PK models based on patient and disease characteristics.

In another study published in 2020, Papamichael et. al. assessed the impact of an upward drift for both infliximab and adalimumab concentrations measured by the homogenous mobility shift assay (HMSA) on clinical care of patients with inflammatory bowel disease. Providers reviewed the individual patient data and drug concentrations before and after the laboratory corrections and then documented whether a different clinical decision would have been made had the corrected drug concentration been originally reported. A multivariable Cox proportional hazards regression analysis was performed to investigate the association of a documented treatment change with treatment failure, defined as drug discontinuation for primary nonresponse, loss of response, or serious adverse event, adjusting for confounding factors. The study population consisted of 479 patients (infliximab, n = 219; adalimumab, n = 260). Upon review, 14.9% (71/479) patients would have had a different treatment decision made had the corrected drug concentration been initially reported. After a median follow-up of 10.6 months, 25.7% of patients (123/479) had treatment failure. A theoretical different clinical decision based on the corrected drug concentrations was not associated with treatment failure (adjusted hazard ratio (HR): 1.452; 95% confidence interval (CI): 0.805-2.618; p = 0.216), which was consistent for both infliximab (adjusted HR: 1.977; 95% CI: 0.695-5.627; p = 0.201) and adalimumab (adjusted HR: 1.484; 95% CI: 0.721-3.054; p = 0.284). The authors concluded that the HMSA infliximab and adalimumab assay drift led to providers reporting a change in care of 15% of patients based on the corrected value. However, these decisions did not lead to a higher rate of treatment failure compared to patients without a retrospective (theoretical) treatment change. There were also significant quantitative and qualitative differences between infliximab and adalimumab concentrations before and after the correction of the HMSA, directly influencing drug concentration thresholds associated with clinical outcomes.

Ungaro and associates looked at IBD patients on maintenance vedolizumab, examining the association of maintenance vedolizumab concentrations with remission in their cross-sectional multi-center study from 2019. A homogeneous mobility shift assay was used to determine trough serum concentrations of vedolizumab and anti-drug antibodies (ATVs). The primary outcome was corticosteroid-free clinical and biochemical remission defined as a composite of clinical remission, normalized C-reactive protein [CRP] and no corticosteroid use in 4 weeks. Secondary outcomes included corticosteroid-free endoscopic and deep remission. Vedolizumab concentrations were compared between patients in remission and with active disease. Logistic regression, adjusting for confounders, assessed the association between concentrations and remission. In total, 258 IBD patients were included (55% CD and 45% UC). Patients in clinical and biochemical remission had significantly higher vedolizumab concentrations (12.7 µg/mL vs 10.1 µg/mL, p = 0.002). Concentrations were also higher among patients in endoscopic and deep remission (14.2 µg/mL vs 8.5 µg/mL, p = 0.003 and 14.8 µg/mL vs 10.1 µg/mL, p = 0.01, respectively). After controlling for potential confounders, IBD patients with vedolizumab concentrations >11.5 µg/mL were nearly 2.4 times more likely to be in corticosteroid-free clinical and biochemical remission. Only 1.6% of patients had ATVs. The authors stated that in a large real-world cohort of vedolizumab maintenance concentrations, IBD patients with remission defined by objective measures (CRP and endoscopy) had significantly higher trough vedolizumab concentrations and immunogenicity was uncommon.

In another study from 2019, a randomized control trial (Hambardzumyan et al.) examined how infliximab-treated patients with rheumatoid arthritis (RA) may respond insufficiently due to low serum infliximab (sIFX) levels, caused by anti-drug antibodies (ADAs). Even though monitoring of sIFX and ADAs is not routinely implemented, and levels for optimal outcome have not been validated. Serum samples of infliximab (sIFX) and anti-drug antibodies (ADAs) levels randomized to methotrexate + infliximab therapy at three, nine, and 21 months were available (n=101). The primary and secondary outcome measures were low disease activity [LDA = 28-joint Disease Activity Score (DAS28) ≤ 3.2] and remission (DAS28 < 2.6). The frequencies of very low sIFX levels increased over time, with 15%, 23%, and 28% at 3, 9, and 21 months from IFX start, respectively, and the majority of patients with very low sIFX levels were ADA positive at these time-points [71% (10/14), 82% (18/22), and 68% (19/28), respectively]. The proportion of patients with LDA was numerically higher at all follow-up time-points among those with sIFX ≥ 0.2 μg/mL compared with patients who had sIFX < 0.2 μg/mL and positive ADAs, although only significant at 21 months (67% and 26%, p=0.002). Similar results were observed when remission was the outcome measure (47% vs 11%, p=0.004). In conclusion, even though monitoring of sIFX and ADAs is not routinely implemented, and levels for optimal outcome have not been validated, these findings support the monitoring of serum drug levels. However, this conclusion requires validation in larger populations and for dose-adjustment studies.

In a 2020 review, Papamichael and Cheifetz presented an analysis on the role of TDM of biologics in patients with IBD. Numerous prospective exposure-response relationship studies and post-hoc analyses of RCTs showed a positive correlation between biologic drug concentrations and favorable clinical outcomes in IBD. These studies also demonstrated that higher drug concentrations appeared to be needed to achieve more stringent objective therapeutic outcomes. Reactive TDM rationalizes the management of primary non-response and secondary loss of response to anti-TNF therapy and is more cost-effective when compared with empiric dose optimization. Additionally, recent data suggest that proactive TDM, with the goal of targeting a threshold drug concentration, is associated with better therapeutic outcomes when compared with empiric dose escalation and/or reactive TDM of infliximab or adalimumab. Finally, proactive TDM can also efficiently guide infliximab de-escalation or discontinuation in patients with IBD in remission. The authors found that reactive TDM is currently considered as standard of care, whereas proactive TDM is emerging as a new therapeutic strategy for better optimizing anti-TNF therapy in IBD. Nevertheless, further data from prospective studies are needed before a wide implementation of TDM-based algorithms in real life clinical practice for newer biologics.

The article by Cheifetz et al from October 2021 reviewed findings from an expert panel and the following consensus was reached: "The panel agreed that reactive TDM (therapeutic drug monitoring) should be used for all biologics for both primary nonresponse and secondary loss of response. It was recommended that treatment discontinuation should not be considered for infliximab or adalimumab until a drug concentration of at least 10–15 μg/mL was achieved. Consensus was also achieved regarding the utility of proactive TDM for anti–tumor necrosis factor therapy. It was recommended to perform proactive TDM after induction and at least once during maintenance. Consensus was achieved in most cases regarding the utility of TDM of biologics in IBD, specifically for reactive and proactive TDM of anti–tumor necrosis factors." However, for the medications that are not anti-TNF drugs the following was noted in the article by Papamichael et al from 2022: "Future studies should also investigate the utility of TDM for biologics other than anti-TNF therapies in both IBD and other immune-mediated inflammatory diseases such as rheumatoid arthritis and psoriasis." Unfortunately this article also noted that multiple "challenges remain and are hindering the widespread implementation of TDM in clinical practice" including identification of the optimal drug concentration to target, the lag time between sampling and results, and the proper interpretation of anti-drug antibody titers among different assays.

Lastly, Hayes conducted a health tech assessment in 2022 regarding the use of anti-infliximab (IFX) antibody (ATI) levels to monitor Infliximab treatment in patients with Crohn disease. Six of the studies evaluated clinical validity of ATI testing and found that they are split between assessments of diagnostic versus prognostic accuracy, definitions of CD response or remission were not consistent across studies. None of the studies involved statistical analysis to determine if competing methods of ATI testing have more accurate methods of detecting or predicting response to IFX treatment. Clinical utility of ATI testing was assessed in 6 additional studies that used divergent protocols for responding to differing ATI levels, varying comparator strategies for management of treatment, and dissimilar definitions of CD response or remission. Also, it should be noted that the use of ATI tests were subject to interference from serum IFX in some of the studies. The authors found that the body of evidence is of very low-quality, the studies have not provided enough corroboration to demonstrate that this technique has adequate diagnostic or prognostic accuracy, nor the capacity to improve management or healthy outcomes of patients. Thus, more robust studies are needed for ATI testing to determine if it shows improved accuracy for diagnosing or predicting response to IFX therapy and if it can improve healthier outcomes and management in patients with CD. In their 2023 annual update of this report, Hayes found only 2 newly published studies that met inclusion (1 prospective observational study and 1 retrospective cohort study). Neither study changed the current rating of very low-quality of evidence. They also found no new or updated guidelines or position statements from relevant organizations.

Applicable Coding

CPT Codes

80145	Adalimumab
80230	Infliximab
80280	Vedolizumab
80299	Quantitation of therapeutic drug, not elsewhere specified
84999	Unlisted chemistry procedure

HCPCS Codes

Not Applicable

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