Measurement of Serum Antibodies to Selected Biologic Agents

Medical Policy #: 02.04.43
Original Effective Date: July 2013
Reviewed: March 2022
Revised: March 2022

DESCRIPTION

Biologic agents (e.g., Infliximab (Remicade), Infliximab biosimilars (Infectra, Renflexis, Avsola), Adalimumab (Humira), Adalimumab biosimilars (Cyltezo), Vedolizumab (Entyvio), Simponi Aria (Golimumab) or Ustekinumab (Stelara)) are used to treat multiple inflammatory conditions, including rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis; inflammatory bowel disease (e.g., Crohn disease, ulcerative colitis), ankylosing spondylitis, and plaque psoriasis. These biologic agents are generally given to patients who fail conventional medical therapy and are typically effective for the induction and maintenance of clinical remission. However, not all patients respond, and a high proportion of patients lose response over time. It is estimated that 1 in 3 patients do not respond to induction biologic therapy (primary nonresponse); further, among initial responders (primary response), response wanes over time in approximately 20% to 60% of patients (secondary nonresponse). 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 antidrug antibodies (ADA).

Detection of Antidrug Antibodies (ADA)
The detection and quantitative measurement of antidrug antibodies (ADA) is difficult owing to drug interference and identifying when antibodies have a neutralizing effect. First generation assays (i.e., enzyme-linked immunosorbent assays (ELISA)) can measure only ADA in the absence of detectable drug levels, due to interference of the drug with the assay. Other techniques available for measuring antibodies include 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 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 inter-study comparisons difficult. One retrospective study in 63 patients demonstrated comparable diagnostic accuracy between 2 different ELISA methods in patients with IBD (i.e., double-antigen ELISA and antihuman lambda chain-based ELISA). This study did not include an objective clinical and endoscopic scoring system for validation results.

Treatment Options for Secondary Nonresponse to Biologic Agents
A diminished or suboptimal response to Infliximab (Remicade) (Infliximab biosimilars: Infectra, Renflexis, Avsola), Adalimumab (Humira) (Adalimumab biosimilars: Cyltezo), Vedolizumab (Entyvio), Simponi Aria (Golimumab) or Ustekinumab (Stelara) can be managed in several ways: shortening the interval between doses, increasing the dose, switching to a different biologic agent (in patients who continue to have loss of response after receiving the increased dose) or switching to a non-biologic agent. Incorporating therapeutic drug monitoring (TMD) into clinical practice has been proposed to allow clinicians to optimize treatment by maintaining effective drug concentrations over time and affecting a patient's loss of response. However, before TDM can be widely applied in clinical practice, there are several obstacles to their regular use including when to use TDM, how to accurately interpret and apply the results of such testing, and in defining the optimal drug concentration thresholds and ranges to target.

The measurement of antibodies to include the measurement of serum drug concentrations (trough levels) to Adalimumab (Humira), (Adalimumab biosimilars: Cyltezo), Infliximab (Remicade), (Infliximab biosimilars: Infectra, Renflexis, Avsola), Vedolizumab (Entyvio), Golimumab (Simponi Aria) or Ustekinumab (Stelara) include but are not limited to the following tests:

- ADALX (Mayo)
- DoseASSURE ADL
- DoseASSURE GOL
- DoseASSURE IFX
- DoseASSURE UST

- Prometheus Anser ADA
- Prometheus Anser IFX
- Prometheus Anser VDZ
- Prometheus Anser UST

Measurement of Serum Antibodies and Serum Levels to Biologic Agents

Clinical Context and Test Purpose
The purpose of testing serum antibodies and serum levels (trough levels) to infliximab (Remicade) (Infliximab biosimilars: Infectra, Renflexis, Avsola), Adalimumab (Humira) (Adalimumab biosimilars: Cyltezo), Vedolizumab (Entyvio), Golimumab (Simponi Aria) or Ustekinumab (Stelara) in patients with arthritis (e.g., rheumatoid, psoriatic, or juvenile idiopathic), inflammatory bowel disease (IBD), ankylosing spondylitis, or plaque psoriasis is to improve health outcomes.

Patients
The relevant populations of interest are individuals with arthritis (e.g., rheumatoid, psoriatic, or juvenile idiopathic), inflammatory bowel disease (IBD), ankylosing spondylitis, or plaque psoriasis.

Patients with these conditions are actively managed by rheumatologists, gastroenterologists, and primary care providers in an outpatient setting.

Interventions
The test considered is testing for serum antibodies and serum levels (trough levels) to Infliximab (Remicade) (Infliximab biosimilars: Infectra, Renflexis, Avsola), Adalimumab (Humira) (Adalimumab biosimilars: Cyltezo), Vedolizumab (Entyvio), Simponi Aria (Golimumab), or Ustekinumab (Stelara)

Comparators
The following practice is currently being used to manage arthritis (e.g., rheumatoid, psoriatic, or juvenile idiopathic), inflammatory bowel disease (IBD), ankylosing spondylitis, or plaque psoriasis: standard of care.

Outcomes
The general outcomes of interest are test validity, change in disease status, health status measures, quality of life, and treatment-related morbidity.

Follow-up over months to years is of interest to the relevant outcomes.

Infliximab (Remicade) and Adalimumab (Humira)
Tumor necrosis factor (TNF) inhibitors (e.g., Infliximab, Adalimumab) are used in the treatment of a number of inflammatory conditions. However, the use of these agents has been associated in some patients with the development of antidrug antibodies (ADA), which may promote adverse effects and diminish drug efficacy. The measurement of

serum antibodies to Infliximab (Remicade) (Infliximab biosimilars: Infectra, Renflexis, Avsola) and Adalimumab (Humira) (Adalimumab biosimilars: Cyltezo) has been proposed to monitor for the formation of antidrug antibodies (ADA) which may cause some patients to become non-responders.

Infliximab (Remicade) is an intravenous tumor necrosis factor (TNF) blocking agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of moderately to severely active rheumatoid arthritis (RA) in combination with methotrexate; moderately to severely active Crohn's disease (CD); moderately to severely active ulcerative colitis; active ankylosing spondylitis (AS); active psoriatic arthritis (PsA); and chronic severe plaque psoriasis.

Adalimumab (Humira) is a subcutaneous tumor necrosis factor (TNF-α) inhibitor that is FDA approved for treatment of: moderately to severely active Crohn's disease (CD); moderately to severely active ulcerative colitis (UC); moderately to severely active rheumatoid arthritis; moderately to severely active polyarticular juvenile idiopathic arthritis (pJIA); active psoriatic arthritis (PsA); active ankylosing spondylitis (AS); moderate to severe plaque psoriasis; moderate to severe Hidradenitis Suppurativa; and non-infectious intermediate posterior and paneuveitis Uveitis (UV).

Infliximab is a chimeric (mouse/human) anti-tumor necrosis factor (TNF-α) monoclonal antibody. Adalimumab is a fully human monoclonal antibody to TNF-α. 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 patient's respond, and high proportion of patients lose response over time. It is estimated that 1 out of 3 patients do not respond to induction therapy (primary nonresponse); further among initial responders, response wanes over time in approximately 20% to 60% of patients (secondary nonresponse). The reasons for therapeutic failures remain a matter of debate but include accelerated drug clearance (pharmacokinetics) and neutralizing agent activity (pharmacodynamics) due to antidrug antibodies (ADA). ADA are also associated with injection site reactions (adalimumab) and acute infusion reactions and delayed hypersensitivity reactions (infliximab).

***Note**: The biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from a biological product already approved by the FDA. Interchangeable biosimilar products can be expected to produce the same clinical result as the reference product in any given patient.*

- *Infliximab Biosimilars: Infectra, Renflexis, Avsola*
- *Adalimumab Biosimilars: Cyltezo*

Measurement of Serum Antibodies and Serum Concentration to Infliximab (Remicade) and Adalimumab (Humira)

Clinically Valid

A test must detect the presence of absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews

In 2012, Lee, et.al. conducted a meta-analysis of patients with inflammatory bowel disease receiving infliximab to estimate the prevalence of ATIs (anti-infliximab antibodies), the effect of immunosuppressants on the prevalence of ATI, the effect of ATIs on the prevalence of infusion reactions and the effect of ATIs on the rates of remission. Databases were searched through October 2011, and 18 studies involving 3326 patients were included. The prevalence of ATIs 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 ATIs (relative risk: 2.07; 95% confidence interval, 1.61-2.67). Immunosuppressants resulted in a 50% reduction in the risk of developing ATIs ($P<0.00001$). The authors concluded, the presence or absence of ATIs did not affect the rates of clinical remission. The prevalence of ATIs depends on the regimen of infliximab administration and the use of immunosuppressants. 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. Further analysis is required to determine whether loss of response is dependent on the titer of ATIs.

Garces et. al. (2013) performed a systematic review and meta-analysis of studies to assess the effect of anti-drug antibodies (ADA) on drug response to infliximab, adalimumab and etanercept, and the effect of immunosuppression on ADA detection, in patients with rheumatoid arthritis (RA), spondylarthritis (SpA), psoriasis and inflammatory bowel diseases (IBD). Databases were searched through August 2012, and out of 2082 studies the reviewers selected 17 studies (1 RCT; 16 observational studies) involving 865 patients (540 with RA, 132 with SpA, 58 with psoriasis, 130 with IBD). The outcomes of interest were a response, which was assessed using random-effect models, sensitivity analysis, meta-regressions and Egger's test and then calculated. Of 865 patients, ADA against infliximab or adalimumab reduced drug response rate by 68% (RR=0.68, 95% CI=0.12 to 0.36), an effect attenuated by concomitant methotrexate (MTX): <74% MTX+: RR=0.23, 95% CI=0.15 to 0.36; ≥74% MTX+: RR=0.32, 95% CI=0.22 to 0.48. Anti-etanercept antibodies were not detected. Of 936 patients, concomitant MTX or azathioprine/mercaptopurine reduced ADA frequency by 47% (RR=0.53, 95% CI=0.42 to 0.67), particularly when ADA were assessed by RIA (RR=0.36, 95% CI=0.23 to 0.55) compared with ELISA (RR=0.63, 95% CI=0.53 to 0.74). The authors concluded, ADA reduces drug response, an effect that can be attenuated by concomitant immunosuppression, which reduces ADA frequency. Drug immunogenicity should be considered for the management of patients receiving biological therapies.

In 2013, Nanda et. al. conducted a meta-analysis of studies that reported on the impact of antibodies to infliximab on clinical outcomes and serum infliximab levels in patients with inflammatory bowel disease (IBD). Antibodies to infliximab (ATIs) have been associated with loss of clinical response and lower serum infliximab (IFX) levels in some studies of patients with inflammatory bowel disease (IBD). This has important implications for patient management and development of novel biologic therapies. The objective of this study was to perform a systematic review and meta-analysis of studies that reported clinical outcomes and IFX levels according to patients' ATI status. Thirteen studies met the inclusion criteria and reported results in 1,378 patients with IBD. All included studies had a high risk of bias in at least one quality domain. The pooled risk ratio (RR) of loss of clinical response to IFX in patients with IBD who had ATIs was 3.2 (95% confidence interval (CI): 2.0-4.9, P<0.0001), when compared with patients without ATIs. This effect estimate was predominantly based on data from patients (N=494) with Crohn's disease (RR: 3.2, 95% CI: 1.9-5.5, P<0.0001). Data only from patients with ulcerative colitis (n=86) exhibited a non-significant RR of loss of response of 2.2 (95% CI: 0.5-9.0, P=0.3) in those with ATIs. Heterogeneity existed between studies, in both methods of ATI detection, and clinical outcomes reported. Three studies (n=243) reported trough serum IFX levels according to ATI status; the standardized mean difference in trough serum IFX levels between groups was -0.8 (95% CI -1.2, -0.4, P<0.0001). A funnel plot suggested the presence of publication bias. The authors concluded, the presence of ATIs is associated with a significantly higher risk of loss of clinical response to IFX and lower serum IFX levels in patients with IBD. Published studies on this topic lack uniform reporting of outcomes. High risk of bias was present in all the included studies.

Meroni et. al. (2015) conducted a systematic analysis to address the pharmacodynamics and pharmacokinetics of tumor necrosis factor (TNF) inhibitors. Databases were searched through March 2013 and studies were stratified by drug, disease area and whether or not concomitant immunosuppressive therapy had been given. All data were tabulated by publication and analyzed descriptively. A total of 57 original research articles were included in the analysis (infliximab n=34; adalimumab n=18; etanercept n=5). There was considerable heterogeneity in study design, methodology for anti-drug antibody detection and drug bioavailability evaluation. Consequently, it was difficult to compare the immunogenic potential of infliximab, adalimumab and etanercept, particularly because different assays with variable sensitivity and specificity were used. The timing of occurrence and the persistence of anti-drug antibodies appeared to be influenced by administration schedules and concomitant immunosuppressive therapy. Monitoring of circulating drug levels and anti-drug antibodies appears to be an emerging and cost-effective strategy for the management of the individual patient. The authors concluded, monitoring drug and anti-drug antibody levels appears to be a putative strategy for optimal and cost-effective intervention. However, studies of consistent and homogeneous design, methodology and duration are warranted to assess the true incidence and consequences of immunogenicity.

In 2015, Thomas et. al. examined the immunogenicity of TNF inhibitors (adalimumab, infliximab, etanercept, golimumab, and certolizumab) in rheumatoid arthritis (RA),

spondyloarthritis (SpA), and inflammatory bowel disease (IBD), and to examine the potential effect of anti-drug antibodies (ADABs) on the loss of clinical response through a systematic literature review and meta-analysis. Databases were searched through December 2013. A total of 68 studies (14,651 patients) matched the inclusion/exclusion criteria. Patients had RA (n=8766), SpA (n=1534), or IBD (n=4351). Overall, the cumulative incidence of ADABs was 12.7 % [95 % confidence interval (CI) 9.5-16.7]. Of the patients using infliximab, 25.3 % (95 % CI 19.5-32.3) developed ADABs compared with 14.1 % (95 % CI 8.6-22.3) using adalimumab, 6.9 % (95 % CI 3.4-13.5) for certolizumab, 3.8 % (95 % CI 2.1-6.6) for golimumab, and 1.2 % (95 % CI 0.4-3.8) for etanercept. ADABs reduced the odds of clinical response by 67 % overall, although most of the data were derived from articles involving infliximab (nine) and adalimumab (eight). The summary effect for infliximab yielded an estimated odds ratio (OR) (with ADABs versus without) of 0.42 (95 % CI 0.30-0.58); the summary effect for adalimumab yielded an estimated odds ratio (OR) (as above) of 0.13 (95 % CI 0.08-0.22); and the odds ratio (OR) (as above) for golimumab was 0.42 (95 % CI 0.22-0.81). All figures were statistically significant. ADABS decreased response by 27 % in RA and 18 % in SpA, both of which were statistically significant. However, the effect of ADABS on response was not statistically significant for IBD when they only included the studies that reported the duration of exposure in the regression analysis. The use of concomitant immunosuppressives (methotrexate, 6-mercaptopurine, azathioprine, and others) reduced the odds of ADAB formation in all patients by 74 %. The odds ratio (OR) for risk with immunosuppressives versus without was 0.26 (95 % CI 0.21-0.32). The authors concluded, ADABs developed in 13 % of patients. All five TNF inhibitors were associated with ADABs, but to varying degrees depending on the specific TNF inhibitor and the disease. ADABs are associated with reduced clinical response and an increased incidence of infusion reactions and injection site reactions. Concomitant use of immunosuppressives can reduce ADAB formation.

Pecoraro et. al. (2017) conducted a systematic review and meta-analysis evaluating the impact of anti-drug antibodies (ADA) on TNFa therapeutic response in patients affected with autoimmune inflammatory disease. Thirty-four studies enrolling 4273 patients was included. Of these, 794 (18.6%) developed ADA. The analysis showed a significant reduction of response (RR 0.43, 95%CI 0.3-0.63) in patients with ADA respect to patients without, especially in patients treated with Infliximab (RR 0.37) or Adalimumab (RR 0.40). Furthermore, the administration of TNFα inhibitors produced a reaction at the infusion site in 17%, infection in 30% and serious AE in 5% of patients. Although ADA significantly reduced TNFa response, the results should be viewed cautiously due to reported study limitations, including small numbers of studies assessed and considerable heterogeneity. Currently, there are many indications about the use of immunogenicity tests to guide the therapy, but information regarding how to implement it in clinical practice is needed.

In 2019, Papamichael et. al., reviewed current data and provided expert opinion regarding the clinical utility of 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 secondary loss of response (SLR) or a serious adverse event.3,4 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. Therapeutic drug monitoring (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. 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, before TDM can be widely applied in clinical practice, there are several obstacles to their regular use including when to use TDM, how to accurately interpret and apply the results of such testing, and in defining the optimal drug concentration thresholds and ranges to target. 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. Moreover, 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. Additional future directions should include the development of accurate, easily accessible, and affordable rapid assays and dashboards to allow fast dosing adaptation and incorporation of predictive PK models based on patient and disease characteristics.

Cohort Studies

While many studies have evaluated the clinical validity using single ADA measurements, at least one assessed their persistence over time. Vande Casteele et. al. (2013) investigates the kinetics of ATI (antibodies to infliximab) formation and drug levels in relation to inflammatory markers and the clinical evolution of the patients. IFX trough and ATI levels were measured retrospectively in 1,232 consecutive serum samples of 90 (64 Crohn's disease and 26 ulcerative colitis) patients, 57 with previously detected and 33 without antibodies with a new homogenous mobility shift assay. Testing with new assay confirmed ATI in 53/90 patients (59%) and 37/90 patients (41%) were ATI negative. In 15/53 patients (28%), ATI disappeared over time whereas in 38/53 patients (72%) ATI persisted. The 26/38 (68%) patients with sustained ATI needed to discontinue IFX treatment compared with 2/15 (13%) patients with transient ATI (relative risk 5.1; 95% confidence interval 1.4-19.0; P=0.0005). An IFX trough level at week 14<2.2 μg/ml

predicted IFX discontinuation due to persistent loss of response (LOR) or hypersensitivity reactions with 74% specificity and 82% sensitivity (likelihood ratio 3.1; P=0.0026). The authors concluded, ATI may be transient and do not always lead to a worse clinical outcome. Sustained high levels of ATI, however, lead to permanent LOR (loss of response). Patients with low IFX trough levels at week 14 are at risk for ATI formation and IFX discontinuation.

Frederiksen et. al. (2014) conducted a single-center retrospective cohort study of inflammatory bowel (IBD) patients treated with infliximab. A notable proportion of patients with inflammatory bowel disease (IBD) are switched from infliximab (IFX) to adalimumab (ADL). Anti-IFX Abs were evaluated in 187 patients treated with IFX as first line anti-TNF agent. Approximately, half (49%) were positive. Detected anti-IFX Abs had functional capacity as judged by a median IFX concentration below limit of detection (interquartile range, 0.0-0.0 μg/mL) versus 3.8 μg/mL (IQR, 1.3-7.9) in anti-IFX Ab-negative patients, $P < 0.0001$; but did not cross-react with ADL. Anti-ADL Abs were assessed in 57 ADL-treated patients. Twelve (21%) tested positive. Patients with previous anti-IFX Ab development were significantly more prone to develop anti-ADL Abs (33%) than those without (0%): odds ratio estimated 11, $P = 0.04$. The anti-ADL Abs were also functional because ADL was undetectable in all anti-ADL Ab-positive patients versus median 8.3 μg/mL (IQR 5.0-11.0) in anti-ADL-negative patients, $P < 0.0001$. The presence of anti-ADL Abs increased the risk of secondary ADL treatment failure with OR 28 (3-248), $P < 0.001$. ADL trough levels, irrespectively of anti-ADL Ab status, associated with efficacy of ADL maintenance therapy: AUC(ROC) 0.77 (0.62-0.93), $P < 0.01$. The authors reported that patients switching from infliximab to adalimumab who had antibodies were more likely to develop ATA. These findings are consistent with other studies and evaluation of ADA using RIA (a strength of this study). Conclusions were limited by the retrospective design and sample size.

In 2015, Jani et. al. investigated whether antidrug antibodies (ADA) and/or drug non-trough levels predict the long-term treatment response in a large cohort of patients with rheumatoid arthritis (RA) treated with adalimumab or etanercept and to identify factors influencing antidrug antibody (ADA) and drug levels to optimize future treatment decisions. A total of 331 patients from an observational prospective cohort were selected (160 patients treated with adalimumab and 171 treated with etanercept). Antidrug antibody levels were measured by radioimmunoassay, and drug levels were measured by enzyme-linked immunosorbent assay in 835 serial serum samples obtained 3, 6, and 12 months after initiation of therapy. The association between antidrug antibodies and drug non-trough levels and the treatment response (change in the Disease Activity Score in 28 joints) was evaluated. Among patients who completed 12 months of follow-up, antidrug antibodies (ADA) were detected in 24.8% of those receiving adalimumab (31 of 125) and in none of those receiving etanercept. At 3 months, antidrug antibody (ADA) formation and low adalimumab levels were significant predictors of no response according to the European League Against Rheumatism (EULAR) criteria at 12 months (area under the receiver operating characteristic curve 0.71 [95% confidence interval (95% CI) 0.57, 0.85]). Antidrug antibody-positive patients received lower median dosages of

methotrexate compared with antidrug antibody-negative patients (15 mg/week versus 20 mg/week; P = 0.01) and had a longer disease duration (14.0 versus 7.7 years; P = 0.03). The adalimumab level was the best predictor of change in the DAS28 at 12 months, after adjustment for confounders (regression coefficient 0.060 [95% CI 0.015, 0.10], P = 0.009). Etanercept levels were associated with the EULAR response at 12 months (regression coefficient 0.088 [95% CI 0.019, 0.16], P = 0.012); however, this difference was not significant after adjustment. A body mass index of ≥30 kg/m(2) and poor adherence were associated with lower drug levels. Although derived from a well-established observational study to examine predictors (genetic and other) of treatment response, ADA serum levels were not used to inform treatment decisions. Study results corroborated other research findings.

Arstikyte et. al. (2015) analyzed the clinical relevance of the levels of TNFα blockers and anti-drug antibodies (anti-drug Ab) in patients with rheumatoid arthritis (RA) and spondylarthritis (SpA) treated with adalimumab (ADA), etanercept (ETA), or infliximab (INF) for a prolonged period of time. Clinical characteristics (disease activity, and adverse events), serum TNFα blockers, and anti-drug Ab levels were evaluated in 62 RA and 81 SpA patients treated with TNFα blockers for a median of 28 months. Anti-ADA Ab was detected in 1 (4.0%) and anti-INF Ab in 14 out of 57 (24.6%) RA and SpA patients. Patient with anti-ADA Ab and 57.1% patients with anti-INF Ab were considered non-responders to treatment. Anti-ETA Ab were not found in any of 61 ETA treated patients. Anti-ADA and anti-INF Ab levels differ between responders and non-responders (P > 0.05). Three (5.3%) patients with high serum anti-INF Ab levels developed infusion related reactions. Patients with anti-INF Ab more often required changing to another biologic drug (OR 11.43 (95% CI 1.08-120.93)) and treatment discontinuation (OR 9.28 (95% CI 1.64-52.52)). Study limitations were the small number of non-responders and lack of specificity on whether any eligible participants declined enrollment.

In 2016, Lombardi et. al. investigated the prevalence of anti-adalimumab antibodies and the association with clinical indexes and tumor necrosis factor (TNF-α) serum levels in psoriatic patients. Patient group I (n=20) receiving biological therapies after switching from adalimumab; patient group II (n=30) ongoing adalimumab therapy; patient group III (n=30) novel adalimumab therapy; patient group IV (n=15) biological therapies other than adalimumab; group V healthy subjects (n=15) never treated with immunosuppressants or biologicals. All groups were tested at enrollment. Group II was also tested at 12 months, and group III at 1, 3 and 6 months. The primary and secondary outcome measures, standard clinical evaluations (Psoriasis Area Severity Index (PASI)), blood samples and two-site ELISA based measurement of serum adalimumab trough levels, anti-adalimumab antibodies and TNF-α. The false positive rate was 23% for anti-adalimumab detection and 22% for anti-adalimumab antibodies in patients naïve to adalimumab. Spurious positivity for anti-adalimumab antibodies (one-time-point positivity in group III during follow-up) accounted for 33% of the total. The prevalence of anti-drug antibodies was highest (87%) in group I patients. No correlations were found between the presence of anti-adalimumab antibodies of adalimumab levels and changes

in PASI scores. There was a high variability of results, high prevalence of false-positives and lack of association between anti-adalimumab antibodies and TNF-α level/PSAI score limit the assay's usefulness. Accurate clinical evaluation is key to early identification of treatment failures.

In 2017, Ara-Martin et. al. examined the relationship between loss of clinical response to anti-tumor necrosis factor (TNF) therapy and the production of anti-drug antibodies (ADAs) and the potential effects of biologic immunogenicity. This observational, non-interventional, cross-sectional study included patients with moderate-to-severe plaque psoriasis and secondary failure of adalimumab, etanercept and infliximab who were seen in the clinical practice setting. Clinical data and blood samples were collected after patient enrollment at the time that next doses of anti-TNF therapy were scheduled. ADA and serum drug concentrations were detected at a central reference laboratory using ELISA. Among 137 enrolled patients, ADA were identified in 31/65 (48%), 0/47 and 8/19 (42%) of patients treated with adalimumab, etanercept and infliximab, respectively. The presence of ADA was associated with a slightly worse clinical response in adalimumab-treated patients (Physician Global Assessment score: 3.7 vs. 3.2, ADA-positive vs. ADA-negative patients [$p < .05$]; correlation between serum ADA titer and body surface area: $r = .292$ [$p = .019$]). Concomitant DMARDs were not associated with anti-TNF immunogenicity in any treatment group. The authors concluded; additional evidence is needed from studies of anti-TNF therapy in psoriasis for clinicians to gain a better understanding of the impact of immunogenicity on clinical response.

Cludts et. al. (2017) conducted a study to develop an antibody assay, applicable for clinical testing, which overcomes the limitation of therapeutic interference and to further determine the relationship between ATA (anti-therapeutic antibodies) development, adalimumab levels and disease activity in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) or ankylosing spondylitis (AS). Use of an electrochemiluminescence platform permitted development of fit-for-purpose immunoassays. Serum samples from patients, taken prior to and at 12 and 24weeks of treatment, were retrospectively analyzed for levels of adalimumab and ATA. Overall, the antibody prevalence was 43.6% at 12weeks and 41% at 24weeks of treatment. Disruption of immune complexes by acid dissociation, a strategy often adopted for this purpose, only marginally increased the antibody prevalence to 48.7% and 46% at 12 and 24weeks respectively. They found that antibody formation was associated with decreasing levels of circulating adalimumab, but no direct effect on disease activity was evident as assessed using DAS28 for RA patients and BASDAI for PsA and AS patients. Study findings are consistent with others, suggesting that adalimumab can serve as an indicator of ATA; however, limitations included small sample size, retrospective research design and failure to confirm neutralization in all ATA-positive samples.

In 2018, Papamichael et. al. investigated drug retention in inflammatory bowel disease (IBD) patients of whom infliximab was optimized to overcome immunogenicity and variables associated with drug retention. This was a retrospective, multicenter study 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 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.

In 2019, Papamichael et. al. reported on a multicenter retrospective cohort study. Patients on maintenance adalimumab therapy from June 2006 to December 2015 were eligible. They analyzed time to treatment failure from start of adalimumab until the end of follow-up [July 2016]. Treatment failure was defined as drug discontinuation for secondary loss of response or serious adverse event or need for IBD-related surgery. Serum adalimumab concentrations and antibodies to adalimumab were measured using the Prometheus homogeneous mobility shift assay. A total of 382 patients with IBD [Crohn's disease, n = 311, 81%] were included and received either at least one proactive TDM [n = 53] or standard of care [empirical dose escalation, n = 279; reactive TDM, n = 50]. Patients were followed for a median of 3.1 years [interquartile range, 1.4-4.8 years]. Multiple Cox regression analyses showed that at least one proactive TDM was independently associated with a reduced risk for treatment failure (hazard ratio [HR]: 0.4; 95% confidence interval [CI]: 0.2-0.9; p = 0.022).

Gomes et. al. (2020) conducted a prospective study to evaluate the quantitative serum level of infliximab (IFX) as well as the detection of anti-infliximab antibodies (ATIs) in patients with Crohn’s disease (CD). The study included adults (n=40) aged 18–70 years in the maintenance phase of IFX therapy. All patients had already received induction therapy (0, two, six weeks), followed by maintenance therapy (5 mg/kg). IFX and ATI levels were analyzed and compared between the patients with active CD (CDA) and those with CD in remission (CDR). Peripheral blood samples were collected just before the new maintenance infusion. The IFX and ATI serum levels were detected using a quantitative ELISA from Promonitors. The study reported no difference in the IFX level between active CD (CDA) and those in remission (CDR) groups (p>0.05). Eighty percent of all patients had IFX levels above the therapeutic concentration (6–10 mg/mL). Two (9%) of the 22 patients with active disease and four (22.2%) of the 18 patients in remission had undetectable levels of IFX. Four (66.6%) of the six patients with undetectable levels of IFX had positive ATI levels; three of these patients were in remission, and one had active disease. In addition, the other two patients with undetectable levels of IFX presented with ATI levels close to the positivity threshold. An author noted limitation of this study was the lack of longitudinal data for the measurement of the IFX and ATI levels over time and over the course of the disease. The authors concluded that the undetectable levels of IFX correlated with the detection of

ATIs, which was independent of disease activity. Immunogenicity was not the main factor for the loss of response to IFX in our study, and the majority of patients in both groups (CDA and CDR) had supratherapeutic levels of IFX.

Grinman et. al., (2020) conducted an observational cross-sectional study that measured serum levels of antiTNF-α biological drugs and their respective antibodies to identify correlations with sustained clinical response, nonresponse, and loss of drug response in IBD patients. Patients (n=95) with Crohn's disease (n=85) or ulcerative colitis (n=10) in maintenance therapy with infliximab (n=63) or adalimumab (n=32) were included. Venous blood samples were harvested in serum tubes immediately before infliximab and adalimumab infusion. Drug trough levels and anti-drug levels were determined using Lisa Tracker Duo Infliximab and Lisa Tracker Duo Adalimumab enzyme-linked immunosorbent assay (ELISA)-based techniques. The authors reported that among the patients with CD, 56 (65.9%) were responders (sustained response), 11 (12.9%) were primary nonresponders (primary failure), and 18 (21.2%) were secondary nonresponders (secondary failure). Among the patients with UC, 7 (70%) were responders, and 3 (30.0%) were secondary nonresponders; there were no reports of patients with UC who were primary nonresponders. Patients with higher C-reactive protein (CRP) levels had significantly lower levels of serum infliximab (p=0.028). Higher concentrations of anti-IFX antibodies were detected among the patients who were not using immunomodulators concomitantly, who had more side effects related to biologicals and who had high levels of CRP (p=0.022, p=0.001, p=0.042; respectively). Lower body mass index (BMI) was significantly associated with higher levels of anti-ADA antibodies (p=0.036), with no significant difference between BMI and anti-IFX antibodies. Patients with adequate serum levels of infliximab present a therapeutic response with decreased levels of inflammatory markers including serum CRP (p=0.033). In contrast, patients with low serum levels of infliximab had high CRP, and anti-infliximab antibodies were present. Patients who had higher serum albumin concentrations also had higher serum levels of infliximab and adalimumab. The results obtained in this IBD cohort study do not show a clear correlation between anti-TNF-α trough levels and immunogenicity (loss of response) with disease outcomes. The authors concluded that the results do not show a clear correlation between anti-TNF-α trough levels and immunogenicity with disease outcomes. However, there were significant associations with BMI, the concomitant use of immunomodulators, the rate of side effects, and laboratory markers, including serum albumin, and CRP. Prospective controlled trials will be necessary to further investigate the most appropriate approaches to monitor patients under biologic therapy, particularly individuals who lose the response.

Summary

A large body of evidence has evaluated the clinical validity of therapeutic drug monitoring (TDM) of biologic agent's infliximab and adalimumab serum drug levels either alone or in combination with measurements of antibodies in inflammatory conditions such as IBD (inflammatory bowel disease). Preliminary data mainly from retrospective studies may 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. Moreover, 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. Additional future directions should include the development of accurate, easily accessible, and affordable rapid assays and dashboards to allow fast dosing adaptation and incorporation of predictive pharmacokinetic (PK) models based on patient and disease characteristic.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would from randomized controlled trials (RCTs).

Several algorithms have been developed for management of patients with IBD (inflammatory bowel disease) or RA (rheumatoid arthritis) who have relapsed during TNF-inhibitor therapy. These algorithms are generally based on evidence that has indicated an association between ADA (antidrug antibodies), reduced serum drug levels, and relapse. None of the algorithms has included evidence demonstrating improved health outcomes, such as reduced time to recovery from relapse (response).

In 2014, Steenholdt et. al. reported results of a non-inferiority trial and cost-effectiveness analysis of 69 patients with CD who relapsed (CDAI ≥220 and/or ≥1 draining perianal fistula) during infliximab therapy. Patients were randomized to infliximab dose intensification (5 mg/kg every 4 weeks) or algorithmic treatment based on serum infliximab level and ATI (antibodies to infliximab): Patients with sub-therapeutic infliximab level (<0.5 μg/mL) had infliximab dose increased if ATI were undetectable or were switched to adalimumab if ATI were detectable; patients with therapeutic infliximab level underwent repeat testing of infliximab and ATI levels if ATI were detectable or diagnostic reassessment if ATI were undetectable. Serum infliximab and ATI levels were measured in all patients using RIA (radioimmunoassay) in single-blind fashion (patients unaware but investigators aware of test results). Randomized groups were similar at baseline; overall, 55 (80%) of 69 patients had nonfistulizing disease. Most patients (70%) had therapeutic serum infliximab levels without detectable ATI; revised diagnoses in 6 (24%) of 25 such patients in the algorithm arm26 included bile acid malabsorption, strictures, and IBS. In both intention-to-treat (ITT) and per-protocol analyses, similar proportions of patients in each randomized group achieved clinical response at week 12, defined as a minimum 70-point reduction from baseline CDAI for

patients with nonfistulizing disease and a minimum 50% reduction in active fistulas for patients with fistulizing disease (ITT, 58% in the algorithm group vs 53% in the control group; p=0.810; per-protocol; 47% in the algorithm group vs 53% in the control group; p=0.781). Only the ITT analysis fell within the prespecified non-inferiority margin of -25% for the difference between groups. Conclusions on the non-inferiority of an algorithmic approach compared with dose intensification from this trial are limited. The non-inferiority margin was arguably large and was exceeded in the conservative per-protocol analysis. Dropouts were frequent and differential between groups; 17 (51%) of 33 patients in the algorithm group and 28 (78%) of 36 patients in the control group completed the 12-week trial. A large proportion of patients (24%) in the algorithmic arm were potentially misdiagnosed (i.e., CD flare was subsequently determined not to be the cause of relapse); the comparable proportion in the control arm was not reported. In most patients (80% who had nonfistulizing disease), only a subjective measure of treatment response was used (minimum 70-point reduction from baseline CDAI).

Roblin et al (2014) conducted a single-center, prospective observational study of 82 patients with inflammatory bowel disease (IBD) (n=45 CD, n=27 UC) with clinical relapse (CDAI >220 or Mayo Clinic >5) during treatment with adalimumab 40 mg every 2 weeks. For all patients, trough adalimumab levels and ADA (antidrug antibodies) were measured in a blinded fashion using ELISA, and adalimumab dose was optimized to 40 mg weekly. Those who did not achieve clinical remission (CDAI <150 or Mayo score <2) within 4 months underwent repeat trough adalimumab and anti-adalimumab antibody testing and were switched to infliximab. Clinical and endoscopic responses after adalimumab optimization and after infliximab therapy for 6 months were compared across 3 groups: (1) those with a therapeutic adalimumab level (>4.9 μg/mL28), (2) those with a sub-therapeutic adalimumab level and undetectable ATA (antibodies to adalimumab); and (3) those with a sub-therapeutic adalimumab level and detectable ATA. After adalimumab optimization, more group 2 patients achieved clinical remission (16 [67%] of 24 patients) than group 1 (12 [29%] of 41 patients; p<0.01 vs group 2) and group 3 (2 [12%] of 17 patients; p<0.01 vs group 2) patients. Duration of remission was longest in group 2 (mean, 15 months) compared with group 1 (mean, 5 months) and group 3 (mean, 4 months; p<0.01 for both comparisons vs group 2). At 1 year, 13 (52%) of 24 patients in group 2 maintained clinical remission compared with no patients in groups 1 or 3 (p<0.01 for both comparisons vs group 2). Results were similar when remission was defined using calprotectin levels (<250 μg/g stool) or endoscopic Mayo score (<2). Fifty-two patients (n=30 CD, n=22 UC) who failed to achieve clinical remission after adalimumab optimization were switched to infliximab. More patients in group 3 achieved clinical remission (12 [80%] of 15 patients) than in group 1 (2 [7%] of 29 patients) or group 2 (2 [25%] of 8 patients; p<0.01 for both comparisons vs group 3). Duration of response after switching to infliximab was longest in group 3 (mean, 14 months) compared with group 1 (mean, 3 months) and group 2 (mean, 5 months; p<0.01 for both comparison vs group 3). At 1 year, 8 (55%) of 15 patients in group 3 maintained clinical remission compared with no patients in groups 1 or 2 (p<0.01 for both comparisons vs group 3). Results were similar using objective measures of clinical remission (calprotectin level, endoscopic Mayo score). These results suggested that

patients with inflammatory bowel disease (IBD) who relapse on adalimumab and have sub-therapeutic serum adalimumab levels may benefit from a higher adalimumab dose if ATA (antibodies to adalimumab) are undetectable or from a change to another TNF inhibitor if ATA are detectable. Relapsed patients who have therapeutic serum adalimumab levels may benefit from change to a different drug class. Strengths of the study include its use of subjective and objective measures of remission and blinded serum drug level and ATA monitoring. However, results were influenced by the small sample size, use of ELISA for antibody testing, and lack of ADA (antidrug antibodies) levels for decision making. Subsequent study comparing the management using the algorithm proposed with usual care is needed. Ideally, using more than 1 method of assaying antibodies would further assessment of analytic validity. Finally, the lead author of the study received lecture fees from the ADA (antidrug antibodies) test provider (Theradiag).

Summary

Convincing evidence for the clinical utility of therapeutic drug monitoring (TDM) in biologic agents for the treatment of inflammatory conditions is currently lacking. 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. 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, before TDM can be widely applied in clinical practice, there are several obstacles to their regular use including when to use TDM, how to accurately interpret and apply the results of such testing, and in defining the optimal drug concentration thresholds and ranges to target. 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. Moreover, 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. Additional future directions should include the development of accurate, easily accessible, and affordable rapid assays and dashboards to allow fast dosing adaptation and incorporation of predictive PK models based on patient and disease characteristics.

Measurement of Serum Antibodies and Serum Concentration to Vedolizumab (Entyvio)

Vedolizumab (Entyvio) is an intravenous tumor necrosis factor blocking agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of moderately to severely active ulcerative colitis (UC); and moderately to severely active Crohn's disease (CD). Vedolizumab is generally given for those patients who have had an inadequate response with lost response to or were intolerant to tumor necrosis factor (TNF) blocker

or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids. This drug is used for achieving clinical response or remission or achieving corticosteroid-free remission.

Serum concentrations of vedolizumab (VDZ) may vary among equally dosed patients which can affect patient outcomes. Some patients may develop immunogenicity (non-response) to VDZ by producing antibodies to vedolizumab and the presence of persistent anti-vedolizumab antibody has been observed to reduce serum concentrations of vedolizumab. Incorporating therapeutic drug monitoring into clinical practice has been proposed to allow clinicians to optimize treatment by maintaining effective drug concentrations over time and affecting a patient's loss of response.

In 2017, Willet et. al. conducted an observational study investigating the association between low trough levels of vedolizumab (Entyvio) during induction therapy for inflammatory bowel disease and need for additional doses within 6 months. The study included 47 patients with Crohn's disease (CD; n = 31) or ulcerative colitis (UC; n = 16) who had not responded to 2 previous treatment regimens with antagonists of tumor necrosis factor and were starting therapy with vedolizumab at 2 hospitals in France, from June 2014 through April 2016. All patients were given a 300-mg infusion of vedolizumab at the start of the study, Week 2, Week 6, and then every 8 weeks; patients were also given corticosteroids during the first 4-6 weeks. Patients not in remission at Week 6 were given additional doses of vedolizumab at Week 10 and then every 4 weeks (extended therapy or optimization). Remission at Week 6 of treatment was defined as CD activity score below 150 points for patients with CD and a partial Mayo Clinic score of < 3 points, without concomitant corticosteroids, for patients with UC. Blood samples were collected each week and serum levels of vedolizumab and antibodies against vedolizumab were measured using an enzyme-linked immunosorbent assay. Median trough levels of vedolizumab and interquartile ranges were compared using the nonparametric Mann-Whitney test. The primary objective was to determine whether trough levels of vedolizumab measured during the first 6 weeks of induction therapy associated with the need for extended treatment within the first 6 months. Based on response to therapy at Week 6, extended treatment was required for 30 of the 47 patients (23 patients with CD and 7 patients with UC). At Week 2, trough levels of vedolizumab for patients selected for extended treatment were 23.0 μg/mL (interquartile range, 14.0-37.0 μg/mL), compared with 42.5 μg/mL in patients who did not receive extended treatment (interquartile range, 33.5-50.7; P = .15). At Week 6, trough levels of vedolizumab <18.5 μg/mL were associated with need for extended therapy (100% positive predictive value, 46.2%; negative predictive value; area under the receiver operating characteristic curve, 0.72) within the first 6 months. Among patients who required extended treatment at Week 10, all of those with trough levels of vedolizumab <19.0 μg/mL at Week 6 had achieved clinical remission 4 weeks later (secondary responders). The authors concluded, patients with CD or UC receiving induction therapy with vedolizumab, low trough levels of vedolizumab at Week 6 (<19.0 μg/mL) are associated with need for additional doses (given at Week 10 and then every 4 weeks). All

patients receiving these additional doses achieved a clinical response 4 weeks later. No subjects reported to have developed antibodies to vedolizumab (ATV) during the study.

In 2018, Ward et. al. reported on current data and future direction on therapeutic drug monitoring of vedolizumab (Entyvio) in inflammatory bowel disease. The introduction of vedolizumab (Entyvio), a lymphocyte adhesion inhibitor, has expanded the relatively limited therapeutic armamentarium available for Crohn's disease and ulcerative colitis. Despite its effectiveness, both primary nonresponse and secondary loss of response to vedolizumab (Entyvio) do occur, as is observed with the use of anti-tumor necrosis factor (TNF) therapy. Further, in a proportion, onset of efficacy may be relatively slow. A large body of data support an exposure–response relationship with anti-TNF drug levels, which has led to therapeutic drug monitoring becoming incorporated into every day clinical management. The influence of patient and disease factors on the pharmacokinetics of anti-TNF levels, including immunogenicity, has also been examined. The role of therapeutic drug monitoring with vedolizumab (Entyvio) is less clear. This review summarizes the available evidence on the pharmacokinetics and pharmacodynamics of vedolizumab in inflammatory bowel disease and how drug levels, immunogenicity and other factors influence clinical outcomes. Vedolizumab (Entyvio) clearance is increased with very high body weight and hypoalbuminaemia but is not influenced by the addition of an immunomodulator. Immunogenicity is uncommon. α4β7 receptor saturation occurs at low serum vedolizumab drug levels, and measuring it alone is insufficient to predict clinical outcomes. Using quartile analysis of vedolizumab drug levels, there appears to be a modest exposure–response relationship during induction. Drug levels at week 6 of approximately >20 μg/ml have been shown to be associated with improved clinical outcomes, including subsequent mucosal healing rates during maintenance and avoiding the need to dose escalate due to lack of response. There are currently insufficient data to support the routine use of therapeutic drug monitoring during maintenance therapy. Further studies to elucidate the role of therapeutic drug monitoring of vedolizumab are needed.

In 2019, Ungaro et. al. examined the association of maintenance vedolizumab concentrations with remission. A cross-sectional multi-center study was performed of inflammatory bowel disease [IBD] patients on maintenance vedolizumab. A homogeneous mobility shift assay [HMSA] 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.

In 2019, Papamichael et. al. reviewed the current data and provided expert opinion regarding the clinical utility of therapeutic drug monitoring (TDM) for biologic therapies in inflammatory bowel disease (IBD). The current evidence supporting the role of therapeutic drug monitoring (TDM) regarding vedolizumab derives only from exposure response relationship studies showing that higher vedolizumab concentrations are associated with better therapeutic outcomes. Although there are emerging data that may show an association between drug concentrations and outcomes, they are not sufficient to guide specific induction and maintenance drug concentrations for vedolizumab. Further RCTs to establish the utility of proactive TDM, particularly during the induction phase, should be performed. Additional future directions should include the development of accurate, easily accessible, and affordable rapid assays and dashboards to allow fast dosing adaptation and incorporation of predictive PK models based on patient and disease characteristics.

Summary
For individuals who have ulcerative colitis (UC) or Crohn's disease (CD) receiving vedolizumab (Entyvio), there is an interest in therapeutic drug monitoring (TMD) not only for the purpose of identifying markers that will serve as end points for successful treatment, but also for timely cessation or switching of therapy in those unlikely to respond. Based on the peer reviewed medical literature the available studies to date are insufficient and have not demonstrated in randomized comparative trials the presence of a clinical utility benefit to therapeutic regimens guided by serum drug levels (trough levels) or measurements of antibodies when compared to standard treatment regimens. Such evidence is necessary to adequately judge clinical response, adverse reactions, and need for a change in therapy.

Further randomized controlled trials (RCTs) are needed to investigate the efficacy of the role of therapeutic drug monitoring (TMD) of vedolizumab (Entyvio). More controlled data is needed to define the best cut-off to define abnormal values of the measured monitor parameters, define optimal thresholds for the different interventions and the subpopulations as to who will benefit the most from this testing. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Measurement of Serum Antibodies and Serum Concentration to Ustekinumab (Stelara)
Ustekinumab (Stelara) is a biologic medication approved by the U.S. Food and Drug Administration (FDA) to lower inflammation and help patients with moderate to severe plaque psoriasis, active psoriatic arthritis and moderately to severely active Crohn's disease. This medication is typically prescribed after non-response to other medications and can be administered subcutaneous or as an IV infusion. Ustekinumab (Stelara) blocks inflammation proteins called IL-12 and IL-23.

Serum concentrations of ustekinumab (Stelara) may vary among equally dosed patients which can affect patient outcomes. Some patients may develop immunogenicity (non-response) by producing antibodies to ustekinumab and the presence of persistent anti-ustekinumab antibody has been observed to reduce serum concentrations of ustekinumab. Incorporating therapeutic drug monitoring into clinical practice has been proposed to allow clinicians to optimize treatment by maintaining effective drug concentrations over time and affecting a patient's loss of response.

Adedokun et. al. (2020) collected data from two phase III randomized controlled trials of patients with ulcerative colitis that evaluated the association between ustekinumab concentration and efficacy, serum based on clinical effects (Mayo score), histologic features, and inflammation (measurement of Creactive protein, fecal calprotectin, and fecal lactoferrin), as well as safety (infections, serious infections, and serious adverse events), during induction and maintenance therapy. The 52-week trial (UNIFI trial) comprised an eight-week, randomized, placebo-controlled, induction study, and a 44-week, randomized-withdrawal, maintenance study. At induction week 0, patients (n=961) randomly (1:1:1) received the following: (1) ustekinumab 130 mg (n=320); (2) ustekinumab weight-range–based dose of approximately 6 mg/kg (n=322); or (3) placebo (n=319). Patients who had a response to induction therapy at eight weeks following administration of intravenous ustekinumab were randomly assigned to receive subcutaneous maintenance injections of 90 mg of ustekinumab (either every 12 weeks [n=172] or every eight weeks [n=176]) or placebo (n=175). Serum samples for ustekinumab drug concentration were collected at all visits during induction (weeks 0, two, four, eight, and 16) and during maintenance (every four weeks through week 44) using a drug-tolerant electrochemiluminescence assay (ECLIA). Anti-drug antibodies were collected during induction (weeks 0, four, eight, and 16) and during maintenance (weeks four, 12, 24, 36, and 44). In the analysis of data from two phase III trials of patients with ulcerative colitis, the authors reported that serum concentrations of ustekinumab were proportional to dose and unaffected by prior biologic or concomitant immunomodulator therapies. Serum concentrations of ustekinumab were associated with clinical and histologic efficacy and markers of inflammation and were not associated with safety events at the doses evaluated. The authors concluded that associations between serum ustekinumab concentration (SUC) and clinical efficacy do not prove cause and effect. A prospective, interventional, longitudinal study is required to address whether trough SUC optimization by TDM improves efficacy outcomes.
In 2019, Papamichael et. al. reviewed the current data and provided expert opinion regarding the clinical utility of therapeutic drug monitoring (TDM) for biologic therapies in inflammatory bowel disease (IBD). The current evidence supporting the role of TDM regarding ustekinumab (Stelara) is based on 2 exposure-response relationship studies showing that higher ustekinumab concentrations correlate to better therapeutic outcomes at this time, there are still no studies comparing either proactive or reactive TDM with empiric ustekinumab optimization. Although there is emerging data that may show an association between drug concentrations and outcomes, they are not sufficient to guide specific induction and maintenance drug concentrations for ustekinumab (Stelara).

Further RCTs to establish the utility of proactive TDM, particularly during the induction phase, should be performed. Additional future directions should include the development of accurate, easily accessible, and affordable rapid assays and dashboards to allow fast dosing adaptation and incorporation of predictive PK models based on patient and disease characteristics.

In 2015, Chiu et. al. conducted a prospective observational study on the association between clinical response to ustekinumab and immunogenicity to ustekinumab prior to adalimumab in 76 patients with plaque psoriasis who were treated with ustekinumab for a minimum of 7 months. Blood samples were drawn just prior to scheduled ustekinumab injection during clinic visits. Levels of anti-ustekinumab antibody (AUA) and serum ustekinumab concentration were measured respectively by radioimmunoassay's and enzyme-linked immunoassays respectively and correlated to clinical data and Psoriasis Area and Severity Index (PASI). AUA was detected in 6.5% of patients after a mean of 13 months of treatment. Patients with positive AUA had significantly lower serum ustekinumab concentrations (0.01 versus 0.2 mg/L, $p<0.001$) and lower PASI50 response than patients without AUA (0% versus 69%, $p = 0.004$). The percentage of AUA formation was comparable between patients who had failed previous adalimumab with or without anti-adalimumab antibodies (AAA) (14.3% versus 12.5%, $p = 1.00$). However, a higher proportion of switchers without AAA obtaining PASI50 (71.4% versus 37.5%) and PASI75 response (42.9% versus 12.5%) within 7 months of ustekinumab treatment than with AAA though this difference did not reach statistical significance.

Summary
There is an interest in therapeutic drug monitoring (TMD) not only for the purpose of identifying markers that will serve as end points for successful treatment, but also for timely cessation or switching of therapy in those unlikely to respond. Based on the peer reviewed medical literature the current evidence supporting the role of therapeutic drug monitoring (TDM) regarding ustekinumab (Stelara) is based on 2 exposure-response relationship studies showing that higher ustekinumab concentrations correlate to better therapeutic outcomes. At this time, there are still no studies comparing either proactive or reactive TDM with empiric ustekinumab optimization. Although there is emerging data that may show an association between drug concentrations and outcomes, they are not sufficient to guide specific induction and maintenance drug concentrations for ustekinumab (Stelara). Further RCTs to establish the utility of proactive TDM, particularly during the induction phase, should be performed. Additional future directions should include the development of accurate, easily accessible, and affordable rapid assays and dashboards to allow fast dosing adaptation and incorporation of predictive PK models based on patient and disease characteristics.

Measurement of Serum Antibodies and Serum Concentration to Simponi Aria (Golimumab)
Golimumab (Simponi Aria) is a fully human monoclonal TNF antibody for the treatment of moderate to severe ulcerative colitis. It should be considered as one of the treatment options when patients have begun failing therapy with mesalamine products or are at risk

for developing steroid dependence. Golimumab is administered subcutaneously (SC) allowing for self-administration and patient independence. To date, little is known about anti-golimumab antibody development and its relation to clinical response in patients with UC. Well-designed studies are needed to expand the existing evidence base to confirm therapeutic drug monitoring (TMD) with biologic agents leads to changes in therapeutic interventions or other changes in disease management that improve patient health outcomes over the long term. Studies should also report how these outcomes compare with adjustments based on patient symptoms, clinical assessment, and standard laboratory evaluation. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Summary of Evidence

The evidence is insufficient to support the use of the therapeutic drug monitoring (TMD) for biologics agents Infliximab (Remicade) (Infliximab biosimilars: Infectra, Renflexis, Avsola), Adalimumab (Humira) (Adalimumab biosimilars: Cyltezo), Vedolizumab (Entyvio), Golimumab (Simponi Aria) or Ustekinumab (Stelara) including but not limited to the following assays: Anser ADA (Adalimuab [Humira]), Anser IFX (Infliximab [Remicade]), Anser UST (Ustekimumab [Stelara]) and Anser VDZ (Vedolizumab [Entyvio]), ADALX (Mayo), DoseASSURE ADL, DoseASSURE GOL, DoseASSURE IFX and DoseASSURE UST in patients with inflammatory conditions (arthritis [e.g., rheumatoid, psoriatic, or juvenile idiopathic], inflammatory bowel disease [IBD], ankylosing spondylitis, or plaque psoriasis) to guide treatment optimization. The overall benefit of therapeutic drug monitoring (TMD) using serum drug levels (trough levels), either alone or in combination with measurement of antibodies has not been established. There is absence of clinical utility studies evaluating if therapeutic drug monitoring (TMD) guided dosing adjustments leads to clinically meaningful changes in patient health outcomes, and how those outcomes compare with adjustments based on patient symptoms, clinical assessment, and standard laboratory evaluation. Well-designed studies are needed to expand the existing evidence base to confirm therapeutic drug monitoring (TMD) with biologic agents leads to changes in therapeutic interventions or other changes in disease management that improve patient health outcomes over the long term. Studies should also report how these outcomes compare with adjustments based on patient symptoms, clinical assessment, and standard laboratory evaluation. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Practice Guidelines and Position Statements

American College of Gastroenterology (ACG)

In 2019, the American College of Gastroenterology (ACG) clinical guideline on ulcerative colitis in adults, recommended against serologic antibody testing to establish or rule out a diagnosis of UC. Perinuclear antineutrophilic cytoplasmic antibody (pANCA) has been identified in up to 70% of UC patients. It has been proposed that using a combination of negative anti–saccharomyces cerevisiae antibodies (ASCA) with elevated pANCA levels facilitates establishing a diagnosis of UC. However, the pooled sensitivity of antibody testing for diagnosis of UC is low, and such markers are not used for

establishing or ruling out a diagnosis of UC. The guideline also stated that patients with moderately to severely active UC who are responders to anti-TNF therapy and now losing response, suggested measuring serum drug levels and antibodies (if there is not a therapeutic level) to assess the reason for loss of response. This is a conditional recommendation based on very low quality of evidence.

In 2018, the American College of Gastroenterology (ACG) clinical guideline on the management of Crohn's disease in adults stated that the routine use of serologic markers of IBD to diagnose Crohn's disease is not indicated. Anti-glycan antibodies are more prevalent in Crohn's disease; however, they have a low sensitivity which makes their use in diagnosis less helpful.

American College of Rheumatology (ACR)
In 2021, the American College Rheumatology (ACR) clinical guideline for the treatment of rheumatoid arthritis did not included recommendations for testing the measurement of serum drug levels (trough levels) either alone or in combination with measurement of antibodies in patients treated with biologic agents for inflammatory conditions.

American Gastroenterological Association (AGA) Institute
In 2017, the American Gastroenterological Association (AGA) issued a guideline on therapeutic drug monitoring in inflammatory bowel disease. Due to paucity of data at the time of publication, this guideline does not address the role of therapeutic drug monitoring (TDM) in patients treated with vedolizumab or ustekinumab. The guideline includes the following recommendations for therapeutic drug monitoring (TMD) in inflammatory bowel disease:

Statement	Strength of Recommendation	Quality of Evidence
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. **Comment**: Of note, there may be a small subset of patients who may still respond by targeting higher target concentrations. Optimal trough	Conditional recommendation	Very low quality

concentrations for induction therapy are uncertain.		
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.	No recommendation	Knowledge gap
In adult patients with IBD being started on thiopurines, the AGA suggests routine TPMT testing (enzymatic activity or genotype) to guide thiopurine dosing. **Comment:** Routine laboratory monitoring, including CBC, should be performed, regardless of TPMT testing results	Conditional recommendation	Low quality
In adult patients treated with thiopurines with active IBD or adverse effects thought to be due to thiopurine toxicity, the AGA suggests reactive thiopurine metabolite monitoring to guide treatment changes. **Comment:** When measuring thiopurine metabolite monitoring in patients with active IBD-related symptoms, we suggest a target 6-thioguanine (6-TGN) cutoff between 230-450 pmol/8 x 108 RBCs when used as	Conditional recommendation	Very low quality

monotherapy; optimal 6-TGN cutoff when thiopurines are used in combination with anti-TNF agents is uncertain		
In adult patients with quiescent IBD treated with thiopurines, the AGA suggests against routine thiopurine metabolite monitoring	Conditional recommendation	Very low quality

Based on the guideline recommendations the below is the suggested target trough concentrations when applying reactive therapeutic drug monitoring in patients with active inflammatory bowel disease on maintenance therapy with anti-tumor necrosis factors:

Drug	Suggested Trough Concentration ug/mL	Comments
Infliximab	>5	Six studies (929 patients) provided data on proportion of patients not in remission above predefined infliximab thresholds (1, 3, 5, 7, and 10 mg/mL). Based on these, proportion of patients not in remission decreased from 25% when using an infliximab threshold of ≥1 mg/mL, to 15% with an infliximab trough concentration of ≥ 3 mg/mL, to approximately 4% with an infliximab trough concentration of ≥ 7 mg/mL or ≥ 10 mg/mL

Adalimumab	≥ 7.5	Four studies provided data on proportion of patients not in remission above adalimumab trough concentration >5.0 ± 1 mg/mL or 7.5 ± 1 mg/mL. On analysis of different thresholds, proportion of patients not in remission progressively decreased from 17% when using an adalimumab threshold ≥ 5.0 ± 1 mg/mL, to 10% with an adalimumab trough concentration of ≥ 7.5 ± 1 mg/mL.
Certolizumab Pegol	≥20	One study provided data from an exposure response pooled analysis from 9 trials. On analysis of different thresholds, proportion of patients not in remission progressively decreased from 42% when using a certerolizumab threshold of ≥10 mg/mL to 26% with a certolizumab trough concentration of ≥20 mg/mL
Golimumab	Unknown	There is a lack of sufficient evidence available to establish a target trough goal

Based on this evidence and target trough concentrations, the panel developed an algorithm for how patients and physicians using shared decision making may respond to reactive therapeutic drug monitoring (TDM) testing. Initially, only the trough concentrations should be assessed. If the level is at or above the target trough, then the patient may consider switching to a different drug class, although escalating index therapy may be a reasonable alternative (especially if reactive TDM is performed in asymptomatic patients with ongoing endoscopic activity, or in patients with perianal disease where target trough concentrations may be higher). In the presence of sufficient trough concentrations, results of antibody testing should not guide treatment decisions.

If the trough concentration is low (below the suggested threshold, in patients with active IBD) and no anti-drug antibodies are present, then the index drug should be optimized using any of the following techniques: shortening the dosing interval and/or increasing the drug dose, and/or adding an immunomodulatory agent. If there is no detectable drug (zero trough concentration) and high-titer anti-drug antibodies are present, then the patient should consider switching to a different drug within the class or to a different drug class. If there is no detectable drug and low-titer antibodies are present, then one can consider trying to optimize the index drug by shortening the dosing interval and/or increasing the drug dose, and/or adding an immunomodulator agent. Typically, optimizing the drug will be attempted before changing to a different drug within the class or switching to a new drug class, although some might opt to change to a different drug within the class or switch to a new drug class. It should be noted that 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

There are several issues that remain unresolved even after assessing the evidence. The best-available evidence did not address the optimal timing for measuring trough concentrations. In most cases, the panel recommends that a trough level for infliximab or adalimumab be drawn as close to the next dose as possible (i.e., within 24 hours). Additionally, while the drug trough concentration is consistent across different commercial assays, assays for anti-drug antibodies are not readily comparable with each other.

When anti-drug antibodies are detected, it is unclear what antibody level is clinically meaningful. Low-titer antibodies may be transient and non-neutralizing, such that shortening the drug-dosing interval and/or escalating the dose may optimize the trough concentration in this setting of low-titer antibodies. In contrast, high-titer anti-drug antibodies, especially with undetectable trough concentrations, are generally persistent and neutralizing. In this setting, especially with undetectable drug, there may be very limited benefit to attempting dose escalation of the index agent and switching to a different drug within the same class may be more effective. Unfortunately, current data do not allow us to identify optimal anti-drug antibody cutoffs for high- vs low-titer antibodies, in the current commercially available assays.

Further studies are needed to better define clinically meaningful versus insignificant anti-drug antibodies, based on titers and/or persistence in repeated testing, and at which titers can anti-drug antibodies be suppressed below needing to change drug therapies.

National Institute for Health and Care Excellence (NICE)
In 2019, the National Institute for Health and Care Excellence (NICE) issued guidance on therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis which included the following recommendations:

- 1.1 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. The ELISA tests covered by this guidance are Promonitor, IDKmonitor, LISA-TRACKER, RIDASCREEN, MabTrack, and tests used by Sanquin Diagnostic Services.

- 1.2 Laboratories currently using ELISA tests for therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis should do so as part of research and further data collection.

- 1.3 Further research is recommended on the clinical effectiveness of using ELISA tests for therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis.

The clinical-effectiveness evidence for ELISA tests for therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis is not robust, although there are some positive trends. The key INGEBIO study is of poor quality and is not generalizable to NHS practice.

In 2016, the National Institute for Health and Care Excellence (NICE) issued guidance on therapeutic monitoring of TNF-α inhibitors in Crohn's disease. NICE recommends the following that laboratory monitoring TNF-α inhibitors in patients with Crohn's disease who have lost response to the treatment, should work with clinicians to collect data through either a prospective study, a local audit, or a registry.

Regulatory Status
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Prometheus ® Laboratories Inc., a College of American Pathologists-accredited lab under CLIA, offers non-radio-labeled, fluid phase homogenous mobility shift assay (HMSA) tests called Anser ™ IFX for infliximab, Anser ™ ADA for adalimumab, Anser ™ VDZ for vedolizumab and Anser™ UST for ustekinumab. These tests are not based on an enzyme-linked immunosorbent assay (EILSA), and each can measure antidrug antibodies in the presence of detectable drug levels, improving upon a major limitation of the ELISA method. These tests measure serum drug concentrations and antidrug antibodies.

DoseASSURE (Labcorp)

- DoseASSURE ADL
- DoseASSURE GOL
- DoseASSURE IFX
- DoseASSURE UST

DoseASSURE biologic monitoring assays:

- Aiding in titrating doses and adjusting frequency to maximize effectiveness.
- Identifying lack of response due to non-compliance or under-treatment.
- Assisting in preventing and managing loss of response due to immunogenicity.
- Predicting which patients are likely to retain long-term response.

ADALX (Mayo) Detection and quantification of antibodies directed against adalimumab in serum. Testing for adalimumab concentration and presence of anti-adalimumab antibodies is helpful to adjust therapeutic strategies for patients starting therapy (proactive monitoring), and to adjust dosing when partial response or loss of response to therapy is observed, manifested as recurrence of symptoms. Enzyme-Linked Immunosorbent Assay (ELISA).

PRIOR APPROVAL

Not applicable.

POLICY

Testing for the measurement of serum drug levels and/or antibodies to monoclonal antibodies, including but not limited to the following anti-tumor necrosis factor (TNF) drugs:

- Infliximab (Remicade) and Infliximab Biosimilars (Infectra, Renflexis, Avsola)
- Adalimumab (Humira) and Adalimumab Biosimilars: (Cyltezo)
- Vedolizumab (Entyvio)
- Ustekinumab (Stelara)
- Simponi Aria (Golimumab); **and**

Performed individually or as part of a panel test for the management of inflammatory conditions (arthritis [e.g., rheumatoid, psoriatic, or juvenile idiopathic], inflammatory bowel disease [IBD], ankylosing spondylitis, or plaque psoriasis), including but not limited to the following are considered **investigational**, because the evidence is insufficient to determine the effects of the technology on net health outcomes:

- ADALX
- DoseASSURE ADL
- DoseASSURE GOL
- DoseASSURE IFX

- DoseASSURE UST
- Prometheus Anser ADA
- Prometheus Anser IFX
- Prometheus Anser VDZ
- Prometheus Anser UST

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- Therapeutic Drug Assays are performed to monitor clinical response to a known, prescribed medication.
    - 80145 Adalimumab
    - 80230 Infliximab
    - 80280 Vedolizumab
- 84999 Unlisted laboratory code (when specified as Prometheus Anser IFX Testing, Prometheus Anser ADA, Prometheus Anser VDZ or Prometheus Anser UST, DoseASSURE ADL, DoseASSURE GOL, DosASSURE IFX, DoseASSURE UST or ADALX)

SELECTED REFERENCES

- Dubeau MF, Ghosh S. Optimizing infliximab therapy for inflammatory bowel disease- the tools are getting sharper. *Gastroenterol Hepatol.* 2012; 8(2):134-6.
- National Institute for Health and Clinical Excellence (NICE). Crohn's disease: management in adults, children and young people. National Institute for Health and Clinical Excellence (NICE); 2012 Oct. 34 p. (NICE clinical guideline; no. 152).
- Dubeau MF, Ghosh S. Optimizing infliximab therapy for inflammatory bowel disease- the tools are getting sharper. *Gastroenterol Hepatol.* 2012; 8(2):134-6. 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.
- Blue Cross and Blue Shield Medical Policy Reference Manual. 2013:5. Accessed 5/20/13.
- Yanai H, Hanauer SB. Assessing response and loss of response to biological therapies in IBD. Am J Gastroenterol 2011; 106:685–698
- Valor L,de la TorreI. Understanding the Immunology Concept Clinical Rheumatology. 2013; 9:1-4
- Prometheus Therapeutics & Diagnostics Anser IFX and Anser ADA. http://www.answerifx.com

- Medscape. Therapeutic Drug Monitoring for Anti-TNF Therapy in Inflammatory Bowel Disease. Released 2/7/2013. https://www.medscape.org/viewarticle/778647
- Intrid Ordas, et al. Therapeutic Drug Monitoring or Tumor Necrosis Factor Antagonist in Inflammatory Bowel Disease. Clinical Gastroenterology and Hepatology 2012; 10:1079-1087
- Gastroenterology & Hepatology August 2013, Volume 9, Issue 8, Supplement 4. Special Meeting Edition, Clinical Research Highlights in IBD: Diagnosis and Anti-Tumor Necrosis Factor Monitoring, Digestive Disease Week 2013.
- American College of Gastroenterology, Management of Crohn's Disease in Adults, 2016.
- American College of Gastroenterology, Ulcerative Colitis Practice Guidelines in Adults, March 2010.
- Roblin X, Rinaudo M, Del Tedesco E, et al. Development of an Algorithm Incorporating Pharmacokinetics of Adalimumab in Inflammatory Bowel Disease. Am J Gastroenterology. Aug 2014;109(8):1250-1256
- Roblin X, Marotte H, et. al. Association Between Pharmacokinetics of Adalimumab and Mucosal Healing in Patients with Inflammatory Bowel Diseases. Clin Gastroenterol Hepatol 2014 Jan 12(1):80-84
- Steenholdt C, Brynskoy J, et. al. Individualized Therapy is More Cost Effective Than Dose Intensification in Patients with Crohn's Disease Who Lose Response to Anti-TNF Treatment: A Randomized Controlled Trial. Gut 2014 June;63(6):919-27
- Steenholdt C, Bendtzen K, et. al. Clinical Implications of Measuring Drug and Anti-Drug Antibodies by Different Assays when Optimizing Infliximab Treatment Failure in Crohn's Disease: Post Hoc Analysis of A Randomized Controlled Trial. Am J Gastroenterology 2014 Jul:109(7):1055-64
- National Institute of Health (NIH), Frank I. Scott, M.D., M.S.C.E and Gary R. Lichtenstein, M.D., Therapeutic Drug Monitoring of Anti-TNF Therapy in Inflammatory Bowel Disease. Curr Treat Options Gastroenterol. 2014 March; 12(1): 59-75
- Bendtzen K. Personalized medicine: theranostics (therapeutics diagnostics) essential for rational use of tumor necrosis factor-alpha antagonists. Discov Med. Apr 2013;15(83):201-211. PMID 23636137
- 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. Sep 2012;18(9):1628-1633. PMID 22038899
- 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. Aug 31, 2012;382(1-2):177-188. PMID 22691619
- 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. May 5, 2013;78-79:39-44. PMID 23454676

- Meroni PL, Valentini G, Ayala F, et al. New strategies to address the pharmacodynamics and pharmacokinetics of tumor necrosis factor (TNF) inhibitors: A systematic analysis. Autoimmun Rev. Sep 2015;14(9):812-829. PMID 25985765
- 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. Dec 2013;72(12):1947-1955. PMID 23223420
- 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. May 27, 2012;24(9):1078-1085. PMID 22647738
- 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. Jan 2013;108(1):40-47; quiz 48. PMID 23147525
- Thomas SS, Borazan N, Barroso N, et al. Comparative Immunogenicity of TNF Inhibitors: Impact on Clinical Efficacy and Tolerability in the Management of Autoimmune Diseases. A Systematic Review and Meta-Analysis. BioDrugs. Aug 2015;29(4):241-258. PMID 26280210
- Arstikyte I, Kapleryte G, Butrimiene I, et al. Influence of Immunogenicity on the Efficacy of Long-Term Treatment with TNF alpha Blockers in Rheumatoid Arthritis and Spondyloarthritis Patients. Biomed Res Int. 2015; 2015:604872. PMID 26064930
- Frederiksen MT, Ainsworth MA, Brynskov J, et al. Antibodies against infliximab are associated with de novo development of antibodies to adalimumab and therapeutic failure in infliximab-to-adalimumab switchers with IBD. Inflamm Bowel Dis. Oct 2014;20(10):1714-1721. PMID 25069030
- Jani M, Chinoy H, Warren RB, et al. Clinical utility of random anti-tumor necrosis factor drug-level testing and measurement of antidrug antibodies on the long-term treatment response in rheumatoid arthritis. Arthritis Rheumatol. May 2015;67(8):2011-2019. PMID 26109489
- Castillo-Gallego C, Aydin SZ, Marzo-Ortega H. Clinical utility of the new ASAS criteria for spondyloarthritis and the disease activity score. Curr Rheumatol Rep. Oct 2011;13(5):395-401. PMID 21748416
- Vande Casteele N, Gils A, Singh S, et al. Antibody response to infliximab and its impact on pharmacokinetics can be transient. Am J Gastroenterol. Jun 2013;108(6):962-971. PMID 23419382
- Eser A, Primas C, Reinisch W. Drug monitoring of biologics in inflammatory bowel disease. Curr Opin Gastroenterol. Jul 2013;29(4):391-396. PMID 23703367
- Khanna R, Sattin BD, Afif W, et al. Review article: a clinician's guide for therapeutic drug monitoring of infliximab in inflammatory bowel disease. Aliment Pharmacol Ther. Sep 2013;38(5):447-459. PMID 23848220

- Lichtenstein GR. Comprehensive review: antitumor necrosis factor agents in inflammatory bowel disease and factors implicated in treatment response. Therap Adv Gastroenterol. Jul 2013;6(4):269-293. PMID 23814608
- Garces S, Antunes M, Benito-Garcia E, et al. A preliminary algorithm introducing immunogenicity assessment in the management of patients with RA receiving tumour necrosis factor inhibitor therapies. Ann Rheum Dis. Jun 2014;73(6):1138-1143. PMID 23666932
- 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. May 2010;105(5):1133-1139. PMID 20145610
- 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. Mar 2011;46(3):310-318. PMID 21087119.
- Tan M. Importance of defining loss of response before therapeutic drug monitoring. Gut. Jul 16, 2014. PMID 25031226
- Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. Mar 2010;105(3):501-523; quiz 524. PMID 20068560
- Lichtenstein GR, Hanauer SB, Sandborn WJ. Management of Crohn's disease in adults. Am J Gastroenterol. Feb 2009;104(2):465-483; quiz 464, 484. PMID 19174807
- Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). May 2012;64(5):625-639. PMID 22473917
- Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis. Mar 2014;73(3):492-509. PMID 24161836
- National Institute for Health and Clinical Excellence (NICE) Therapeutic monitoring of TNF-alpha inhibitors in Crohn's disease. Diagnostic guidance DG22 Published date February 2016. Also available at https://www.nice.org
- Jasvinder A, Singh K, Saag S, et. al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care & Research DOI 10.1002/acr.22783
- UpToDate. Tumor necrosis factor alpha inhibitors: induction of antibodies, autoantibodies and autoimmune disease. Klaus Bendtzen M.D., DMSc. Topic last updated August 4, 2015. Also available at https://www.uptodate.com
- UpToDate. Adalimumab for treatment of Crohn disease in adults. Robert M. Penner BSc, M.D., FRCPC, MSc, Richard N. Fedorak M.D., FRCPC. Topic last updated December 16, 2015. Also available at https://www.uptodate.com
- UpToDate. Infliximab in Crohn disease. Richard P MacDermott M.D., Gary R. Lichtenstein M.D., Topic last updated July 9, 2015. Also available at https://www.uptodate.com

- UpToDate. Overview of the management of Crohn disease in children and adolescents. Athos Bousvarous M.D. Topic last updated February 21, 2017. Also available at https://www.uptodate.com
- UpToDate. Treatment of psoriasis. Steven R. Feldman M.D., PhD. Topic last updated January 11, 2017. https://www.uptodate.com
- UpToDate. Assessment and treatment of ankylosing spondylitis in adults. David T. Yu, M.D. Topic last updated April 21, 2016. Also available at https://www.uptodate.com
- Hernandez-Breijo B, Chaparro m, Cano-Martinez D, et. al. Standardization of the homogenous mobility shift assay protocol for evaluation of anti-infliximab antibodies. Application of the method to Crohn's disease patients treated with infliximab. Biochem Pharmacol. Sep 21, 2016. PMID 27664854
- Moore C, Corbett G, Moss A. Systematic review and meta-analysis: Serum infliximab levels during maintenance therapy and outcomes in inflammatory bowel disease. Journal of Crohn's and Colitis 2016 619-625.
- Magro F, Rodrigues-Pinto E, Santos-Antunes J, et. al. High C-reactive protein in Crohn's disease patients predicts nonresponse to infliximab treatment. J Crohns Colitis 2014;8(2):129-36
- Sandborn WJ, Colombel JF, D'Haens G, et. al. Association of baseline C-reactive protein and prior anti-tumor necrosis factor therapy with need for weekly dosing during maintenance therapy with adalimumab in patients with moderate to severe Crohn's disease. Curr Med Res Opin 2013;29(5):483-93
- Shelton E, Allegretti JR, Stevens B, et. al. Efficacy of vedolizumab as induction therapy in refractory IBD patients: A multi-center cohort. Inflamm Bowel Dis. 2015 Aug 17. MPID 26288002
- Prometheus Anser VDZ. Also available at https://www.anserifx.com
- Entyvio. Drugs.com https://www.drugs.com/entyvio.html
- Raine T. Vedolizumab for inflammatory bowel disease: Changing the game, or more of the same? United European Gastroenterology 2014 Vol. 2(5) 333-344
- Ben-Horin S, et. al. Optimizing Biologic Treatment in IBD: Objective Measures, but When, How, and How Often? BMC Gastroenterology 2015;15(178) 1-7
- Feagan BG, Rutgeerts P, Sands BE, et. al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2013; 369: 699-710
- Sanborn WJ, Feagan BG, Rutgeerts P, et. al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 2013; 369:711-721
- Sands BE, Feagan BG, Rutgeerts P, et. al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment had failed. Gastroenterology 2014; 147: 618-627
- UpToDate. Approach to the Adult with Chronic Diarrhea in Rich Settings. Peter A. L. Bonie M.D., J. Thomas Lamont M.D., Topic last updated June 5, 2017. Also available at https://www.uptodate.com
- UpToDate. Approach to the Diagnosis of Chronic Diarrhea in Children in Resource Rich Countries. Richard Kellemayer M.D., PhD, Robert J. Shulman M.D., Topic last updated May 17, 2016. Also available at https://www.uptodate.com

- UpToDate. Clinical Manifestations, Diagnosis and Prognosis of Crohn's Disease in Adults. Mark A. Peppercorn M.D., Sunanda V. Kane M.D., MSPH, Topic last updated April 25, 2017. Also available at https://www.uptodate.com
- UpToDate. Overview of the Medical Management of Mild to Moderate Crohn Disease in Adults. Richard J. Farrell M.D., Mark A. Peppercorn M.D., Topic last updated July 28, 2016. Also available at https://www.uptodate.com
- UpToDate. Overview of the Medical Management of Severe or Refractory Crohn Disease in Adults. Richard J. Farrell M.D., Mark A. Peppercorn M.D., Topic last updated November 28, 2016. Also available at https://www.uptodate.com
- UpToDate. Clinical Manifestations, Diagnosis, and Prognosis of Ulcerative Colitis in Adults. Mark A. Peppercorn M.D, Sunanda V. Kane M.D., MSPH, Topic last updated September 7, 2016
- UpToDate. Management of Mild to Moderate Ulcerative Colitis in Adults. Richard P. MacDermott M.D., Topic last updated June 13, 2017. Also available at https://www.uptodate.com
- UpToDate. Management of Severe Ulcerative Colitis in Adults. Mark A. Peppercorn M.D., Richard J. Farrell M.D., Topic last updated September 6, 2016. Also available at https://www.uptodate.com
- UpToDate. Approach to Adults with Steroid Refractory and Steroid Dependent Ulcerative Colitis. Russell D. Cohen M.D., FACG, AGAF, Adam C. Stein M.D., Topic last updated May 30, 2017. Also available at https://www.uptodate.com
- UpToDate. Management of Mild to Moderate Ulcerative Colitis in Children and Adolescents. Athos Bousvaros M.D., Mala Setty M.D., Jess L. Kaplan M.D., Topic last updated June 27, 2017. Also available at https://www.uptodate.com
- UpToDate. Management of Severe or Refractory Ulcerative Colitis in Children and Adolescents. Athos Bousvaros M.D., Mala Setty M.D., Jess L. Kaplan M.D., Topic last updated June 13, 2017. Also available at https://www.uptodate.com
- UpToDate. Anti-Tumor Necrosis Factor Therapy in Ulcerative Colitis. Yousif I A-Rahim M.D., PhD, Richard J. Farrell M.D., Topic last updated March 24, 2015. Also available at https://www.uptodate.com
- Hernandez-Breijo B, Chaparro M, Cano-Martinez D, et al. Standardization of the homogeneous mobility shift assay protocol for evaluation of anti-infliximab antibodies. Application of the method to Crohn's disease patients treated with infliximab. Biochem Pharmacol. Dec 15 2016; 122:33-41. PMID 27664854
- Steenholdt C, Brynskov J, Thomsen OO, et al. Individualized therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomized, controlled trial. Gut. Jun 2014;63(6):919-927. PMID 23878167
- Pecoraro V, De Santis E, Melegari A, et al. The impact of immunogenicity of TNFalpha inhibitors in autoimmune inflammatory disease. A systematic review and meta-analysis. Autoimmun Rev. Jun 2017;16(6):564-575. PMID 28411169
- Cludts I, Spinelli FR, Morello F, et al. Anti-therapeutic antibodies and their clinical impact in patients treated with the TNF antagonist adalimumab. Cytokine. Aug 2017; 96:16-23. PMID 28279855

- Ara-Martin M, Pinto PH, Pascual-Salcedo D. Impact of immunogenicity on response to anti-TNF therapy in moderate-to-severe plaque psoriasis: results of the PREDIR study. J Dermatolog Treat. Nov 2017;28(7):606-612. PMID 28274164
- Lombardi G, Perego S, Sansoni V, et al. Anti-adalimumab antibodies in psoriasis: lack of clinical utility and laboratory evidence. BMJ Open. Dec 09 2016;6(12): e011941. PMID 27940624
- Vande Casteele N, Herfarth H, Katz J, et. al. American Gastroenterological Association Institute technical review on the role of therapeutic drug monitoring in the management of inflammatory bowel diseases. Gastroenterology 2017; 153:835-857
- Colombel JF, Narula N, Peyrin-Biroulet L. Management strategies to improve outcomes of patients with inflammatory outcomes of patients with inflammatory bowel diseases. Gastroenterology 2017: 152:351-361 e5
- Paul S, Del Tedesco E, Marotte H, et. al. Therapeutic drug monitoring of infliximab and mucosal healing in inflammatory bowel disease: a prospective study. Inflamm Bowel Dis 2013; 19:2568-2576
- Yanai H, Lichtensteine L, Assa A, et. al. Levels of drug and antidrug antibodies are associated with outcome of interventions after loss of response to infliximab or adalimumab. Clin Gastroenterol Hepatol 2015; 13:522-530
- Ungar B, Levy I, Yavne Y, et. al. Optimizing anti-TNF-a therapy: serum levels of infliximab and adalimumab are associated with mucosal healing in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2016; 14:550-557 e2
- Bortlik M, Duricova D, Malickova K, et. al. Infliximab trough levels may predict sustained response to infliximab in patients with Crohn's disease. J Crohns Colitis 2013; 7:763-743
- Singh N, Rosenthal CJ, Melmed GY, et.al. Early infliximab trough levels are associated with persistent remission in pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis 2014; 20:1708-1713
- Warman A, Straathof JWA, Derijks LJJ. Therapeutic drug monitoring of infliximab in inflammatory bowel disease patients in teaching hospital setting. Results of a prospective cohort study. Eur J Gastroenterol Hepatol 2015; 27:242-248
- Mazor Y, Almog R, Kopylov U, et. al. Adalimumab drug and antibody levels as predictors of clinical and laboratory response in patients with Crohn's disease. Ailment Pharmacol Ther 2014; 40:620-628
- Ward MG, Kariyawasam VC, Mogan SB, et. al. Clinical utility of measuring adalimumab trough levels and antibodies to adalimumab in patients with inflammatory bowel diseases. J Gastroenterol Hepatol 2013; 28:100-101
- Vande Casteele N, Ferrante M, Van Assche G, et. al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology 2015; 148:1320-1329
- Feruerstein J, Nguyen G, Kupfer S, et. al. American Gastroenterological Association Institute Guideline on the therapeutic drug monitoring in inflammatory bowel disease. Gastroenterology 2017; 153:827-834

- Bendtzen K. Personalized medicine: theranostics (therapeutics diagnostics) essential for rational use of tumor necrosis factor-alpha antagonists. Discov Med. Apr 2013;15(83):201-211. PMID 23636137
- Prometheus Therapeutics and Diagnostics – Prometheus Anser UST. Also available at https://www.anserifx.com
- Prometheus Laboratories Inc. New Test Monitors Therapeutic Ustekinumab Levels in IBD Patients. Also available at https://www.prnewswire.com
- FDA Highlights of Prescribing Information – Ustekinumab (Stelara). Also available at https://www.accessdata.fda.gov
- Battat R, Kopvlov U, Bessissow T, et. wl. Association between ustekinumab trough concentrations and clinical biomarker, and endoscopic outcomes in patients with Crohn's disease. Clin Gastroenterol Hepatol 2017 Sep;15(9):1427-1434. PMID 28365485
- Detrez I, Dreesen E, Van Stappen T, et. al. Variability in Golimumab Exposure: A real-life observational study in active ulcerative colitis. J Crohns Colitis 2016 May:10(5):575-81. PMID 26738756
- Chui HY, Chu TW, Cheng YP, et. al. The association between clinical response to ustekinumab and immunogenicity to ustekinumab and prior adalimumab. PloS One 2015 Nov 13;10(11):e0142930. PMID 26566272
- Bar-Yoseph H, Levhar N, Selinger L, et. al. Early drug and anti-infliximab antibody levels for prediction of primary nonresponse to infliximab therapy. Aliment Pharmacol Ther 2018 Jan;47(2):212-218. PMID 29124774
- Bartelds GM, Krieckaert CL, 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 Apr 13;305(14):1460-8. PMID 21486979
- Bartelds GM, Wijbrandts CA, Nurmohamed MT, et. al. Anti-infliximab and anti-adalimumab antibodies in relation to response to adalimumab in infliximab switchers and anti-tumor necrosis factor naïve patients: a cohort study. Ann Rheum Dis 2010 May;69(5):817-21. PMID 19581278
- 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 Jul;77(4):313-8. PMID 20471890
- Kelly OB, Donnell SO, Stempak JM, et, al. Therapeutic drug monitoring to guide infliximab dose adjustment is associated with better endoscopic outcomes than clinical decision making alone in active inflammatory bowel disease. Inflamm Bowel Dis 2017 Jul;23(7):1202-1209. PMID 28498155
- Koga A, Matsui T, Takatsu N, et. al. Trough levels of infliximab is useful for assessing mucosal healing in Crohn's disease: a prospective cohort study. Intest Res 2018 Apr 1692):223-232. PMID 29743835
- Manerio JR, Salgado E, Gomez-Reino JJ. Immunogenicity of monoclonal antibodies tumor necrosis factor used in chronic immune-mediated inflammatory conditions: systematic review and meta-analysis. JAMA Intern Med 2013 Aug 12;173(15):1416-28. PMID 23797343

- Martinez-Feito A, Plasencia-Rodriguez C, Navarro-Compan V, et. al. Optimal concentration range of golimumab in patients with axial spondyloarthritis. Clin Exp Rheumatol 2018 Jan-Feb;36(1):110-114. PMID 28980904
- Merras-Salmio, Kolho KL. Clinical use of infliximab trough levels and antibodies to infliximab in pediatric patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2017 Feb;64(2):272-278. PMID 27149256
- Ohem J, Hradsky O, Zarubova K, et. al. Evaluation of infliximab therapy in children with Crohn's disease using trough levels predictors. Dig Dis 2018;36(1):40-48. PMID 28817809
- Pascual-Salcedo D, Plasencia C, Ramiro S, et. al. Influence of immunogenicity on the efficacy of long-term treatment with infliximab in rheumatoid arthritis. Rheumatology (Oxford) 2011 Aug;50(8):1445-52. PMID 21427177
- Plasencia C, Pascual-Salcedo D, Nurio L, et. al. Influence of immunogenicity on the efficacy of long-term treatment of spondyloarthrosis with infliximab. Ann Rheum Dis 2012 Dec;71(12):1955-60. PMID 22563028
- Ungar B, Chowers Y, Yavzori M, et. al. The temporal evolution of antidrug antibodies in patients with inflammatory bowel disease treated with infliximab. Gut 2014 Aug;63(8):1258-64. PMID 24041539
- Ungar B, Engel T, Yablecovitch D, et. al. Prospective observational evaluation of time-dependency of adalimumab immunogenicity and drug concentrations: the POETIC Study. Am J Gastroenterol 2018 Jun;113(6):890-898.
- Vande Casteel N, Ferrante M, Van Assche G, et. al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology 2015; 148:1320-1329
- Vande Casteele N, Khanna R, Levesque BG, et. al. The relationship between infliximab concentrations, antibodies to infliximab and disease activity in Crohn's disease. Gut 2015 Oct;64(10):1539-45. PMID 25336114
- Willet N, Boschetti G, Fovet M, et. al. Association between low trough levels of vedolizumab during induction therapy for inflammatory bowel disease and need for additional doses within 6 months. Clin Gastrointerol Hepatol 2017 Nov;15(11):1750-1757. PMID 27890854
- Ungar B, Kopvlov U, Yavzori M, et. al. Association of vedolizumab level, anti-drug antibodies, and a4B7 occupancy with response in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol 2018 May;16(5):697-705. PMID 29223444
- Dreesen E, Verstockt B, Bian S, et. al. Evidence to support monitoring of vedolizumab trough concentrations in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol 2018 Dec;16(12):1937-1946. PMID 29704680
- Freeman K, Taylor-Phillips S, Connock M, et. al. Test accuracy of drug and antibody assays for predicting response to antitumor necrosis factor treatment of Crohn's disease: a systematic review and meta-analysis. BMJ Open 2017;7(6):e014581
- National Institute for Health and Clinical Excellence (NICE) Therapeutic Monitoring of TNF-alpha Inhibitors in Crohn's Disease (LISA-Tracker ELISA

Kits, IDKmonitor ELISA Kits, and Promonitor ELISA Kits). Diagnostic Guidance (DG22). Published February 2016. Also available at https://www.nice.org
- Vermeire S, Gils A, Accossato P, et al. Immunogenicity of biologics in inflammatory bowel disease. Therap Adv Gastroenterol. 2018; 11:1-13
- Casteele NV, Herfarth H, Katz J, et al. American Gastroenterological Association Institute technical review on the role of therapeutic drug monitoring in the management of inflammatory bowel diseases. Gastroenterology. 2017; 3:835-57
- Zheng MK, Shih DQ, Chen GC. Insights on the use of biosimilars in the treatment of inflammatory bowel disease. World J Gastroenterol. 2017;23(11):1932
- Papamichael K, Cheifetz AS, Melmed GY, et al. Appropriate therapeutic drug monitoring of biologic agents for patients with inflammatory bowel diseases [published online ahead of print March 27, 2019]. Clin Gastroenterol Hepatol. Doi: 10.1016/j.cgh.2019.03.037
- Bodini G, Giannini EG, Savarino V, et al. Infliximab trough levels and persistent vs transient antibodies measured early after induction predict long-term clinical remission in patients with inflammatory bowel disease. *Dig Liver Dis*. 2018;50(5):452-456
- Papamichael K, Vajravelu RK, Osterman MT, Cheifetz AS. Long-term outcome of infliximab optimization for overcoming immunogenicity in patients with inflammatory bowel disease. Dig Dis Sci. 2018;63(3):761-767
- Wright EK, Kamm MA, De Cruz P, et al. Anti-tnf therapeutic drug monitoring in post-operative Crohn's disease. J Crohns Colitis. 2018;12(6):653-661
- Papamichael K, Juncadella A, Wong D, et al. Proactive therapeutic drug monitoring of adalimumab is associated with better long-term outcomes compared to standard of care in patients with inflammatory bowel disease. J Crohns Colitis. 2019;13(8):976-981
- Ungaro RC, Yarur A, Jossen J, et al. Higher trough vedolizumab concentrations during maintenance therapy are associated with corticosteroid-free remission in inflammatory bowel disease. J Crohns Colitis. 2019;13(8):963-969
- Papamichail K, Clarke WT, Casteele NV, et al. Comparison of assays for therapeutic monitoring of infliximab and adalimumab in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2020; S1542-3565(20):30273-30271
- Papamichael, K. and A. S. Cheifetz. Therapeutic drug monitoring in patients on biologics: lessons from gastroenterology. Curr Opin Rheumatol 2020 32(4): 371-379
- Papamichael, K., et al. Long-Term Outcome of Infliximab Optimization for Overcoming Immunogenicity in Patients with Inflammatory Bowel Disease. Dig Dis Sci 2018 63(3): 761-767
- Papamichael, K., et al. Clinical Impact of Corrections to Infliximab and Adalimumab Monitoring Results with the Homogeneous Mobility Shift Assay. J Clin Med 2020 9(9)
- Van den Berghe, N, Verstockt, B, Tops, S, Ferrante, M, Vermeire, S, Gils, A. Immunogenicity is not the driving force of treatment failure in vedolizumab-treated

inflammatory bowel disease patients. Journal of gastroenterology and hepatology.2019 Jul;34(7):1175-81. PMID: 30589948
- FDA Biosimilar Products. https://www.fda.gov/drugs/biosimilars/biosimilar-product-information
- Rubin D, Ananthakrishnan A, Siegel C, et. al. ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol 2019; 114:384-413
- Lichtenstein G, Loftus E, Isaacs K, et. al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. AM J Gastroenterol advance online publication 27, March 2018; doi:10.1038/ajg.2018.27
- Assa A, Matar M, Turner D, Broide E, Weiss B, Ledder O, et al. Proactive Monitoring of Adalimumab Trough Concentration Associated with Increased Clinical Remission in Children with Crohn's Disease Compared With Reactive Monitoring. Gastroenterology. 2019 Oct;157(4):985-996.e2
- Gomes LEM, da Silva FAR, Pascoal LB, Ricci RL, Nogueira G, Camargo MG, et al. Serum Levels of Infliximab and Anti-Infliximab Antibodies in Brazilian Patients with Crohn's Disease. Clinics (Sao Paulo). 2019 Apr 8;74: e824
- Grinman AB, de Souza MDGC, Bouskela E, Carvalho ATP, de Souza HSP. Clinical and laboratory markers associated with anti-TNF-alpha trough levels and anti-drug antibodies in patients with inflammatory bowel diseases. Medicine (Baltimore). 2020 Mar;99(10): e19359
- Hanžel J, Sever N, Ferkolj I, Štabuc B, Smrekar N, Kurent T, et al. Early vedolizumab trough levels predict combined endoscopic and clinical remission in inflammatory bowel disease. United European Gastroenterol J. 2019 Jul;7(6):741-749
- Kennedy NA, Heap GA, Green HD, Hamilton B, Bewshea C, Walker GJ, et al. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. Lancet Gastroenterol Hepatol. 2019 May;4(5):341-353
- Sánchez-Hernández JG, Rebollo N, Martin-Suarez A, Calvo MV, Muñoz F. A 3-year prospective study of a multidisciplinary early proactive therapeutic drug monitoring programme of infliximab treatments in inflammatory bowel disease. Br J Clin Pharmacol. 2020 Jun;86(6):1165-1175
- Sands BE, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johanns J. Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2019 Sep 26;381(13):1201-1214
- Shah R, Hoffman GR, El-Dallal M, Goldowsky AM, Chen Y, Feuerstein JD. Is Therapeutic Drug Monitoring for Anti-Tumor Necrosis Factor Agents in Adults with Inflammatory Bowel Disease Ready for Standard of Care? A Systematic Review and Meta-analysis. J Crohns Colitis. 2020 Feb 17: jjaa02
- Soufflet N, Boschetti G, Roblin X, Cuercq C, Williet N, Charlois AL, Duclaux-Loras R, Danion P, Mialon A, Faure M, Paul S, Flourie B, Nancey S. Concentrations of Ustekinumab During Induction Therapy Associate with Remission in Patients With Crohn's Disease. Clin Gastroenterol Hepatol. 2019 Nov;17(12):2610-2612

- Fraenkel L, Bathon J, England B, et. al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care & Research Vol. 73, No.7, July 2001, pp 924-939

POLICY HISTORY

Date	Reason	Action
March 2022	Annual Review	Policy Revised
March 2021	Annual Review	Policy Revised
March 2020	Annual Review	Policy Revised
March 2019	Annual Review	Policy Revised
March 2018	Annual Review	Policy Revised
July 2017	Interim Review	Policy Revised
March 2017	Annual Review	Policy Revised
March 2016	Annual Review	Policy Revised
April 2015	Annual Review	Policy Revised
May 2014	Annual Review	Policy Revised
July 2013		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

*CPT® is a registered trademark of the American Medical Association.