02.04.43 Measurement of Serum Antibodies to Selected Biologic Agents

Original Effective Date: July 2013

Review Date: February 2026

Revised: February 2024

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Related Policies:

- None

Summary

Description

Biologic agents (e.g., Infliximab [Remicade], Infliximab biosimilars [Inflectra, Renflexis, Avsola, Zymfentra], Adalimumab [Humira], Adalimumab biosimilars [Cyltezo], Vedolizumab [Entyvio], Simponi Aria [Golimumab], Certolizumab [Cimzia], Etanercept [Enbrel] or Ustekinumab [Stelara], Ustekinumab biosimilars [Pyzchiva, Selarsdi, Stegeyma, Wezlana, Yesinktek]) are used to treat multiple inflammatory conditions, including but not limited to rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis; inflammatory bowel disease (e.g., moderate to severely active Crohn's disease [CD] or ulcerative colitis [UC]), ankylosing spondylitis, and moderate to severe plaque psoriasis. Following the primary response to

these medications, some individuals become secondary nonresponders. The development of antidrug antibodies is considered a cause of this secondary nonresponse.

Summary of Evidence

For individuals who have rheumatoid arthritis, psoriatic arthritis or juvenile idiopathic arthritis; inflammatory bowel disease (e.g., moderate to severely active CD or UC); ankylosing spondylitis; and moderate to severe plaque psoriasis who receive evaluation of serum antibodies related to biologic agents (e.g., Infliximab [Remicade], Infliximab biosimilars [Inflectra, Renflexis, Avsola, Zymfentra]), Adalimumab [Humira], Adalimumab biosimilars [Cyltezo], Vedolizumab [Entyvio], or Ustekinumab ([Stelara], Ustekinumab biosimilars [Pyzchiva, Selarsdi, Stegeyma, Wezlana, Yesinktek]), the evidence includes multiple systematic reviews, randomized controlled trials (RCTs) and observational studies. Relevant outcomes are test validity, change in disease status, health status measures, quality of life (QOL), and treatment-related morbidity. Antibodies to biologic agents develop in a substantial proportion of treated individuals and are believed to neutralize or enhance clearance of the drugs. Considerable evidence has demonstrated an association between antidrug antibodies and secondary nonresponse as well as injection-site and infusion-site reactions. The clinical usefulness of measuring antidrug antibodies hinges on whether test results inform management changes, thereby leading to improved outcomes, compared with management directed by symptoms, clinical assessment, and standard laboratory evaluation. Limited evidence has described management changes after measuring antidrug antibodies. A RCT did not find a difference in relapse rates with therapeutic drug monitoring of Infliximab using trough levels and ADA compared to standard therapy without monitoring these levels. A small RCT in individuals with CD and other inflammatory diseases comparing ADA-informed management of relapse with standard dose escalation did not demonstrate improved outcomes with the ADA-informed approach. Additionally, many assays, some having significant limitations, have been used in studies; ADA threshold values that are informative for discriminating treatment responses have not been established. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with moderate to severely active CD, rheumatoid arthritis, psoriatic arthritis and moderate to severe plaque psoriasis who receive evaluation of serum antibodies related to biologic agent to Certolizumab (Cimzia), the evidence includes case studies. Relevant outcomes are test validity, change in disease status, health status measures, QOL, and treatment-related morbidity. There is currently a paucity of evidence in the published peer reviewed medical literature evaluating the effectiveness of measuring ADA of anti-tumor necrosis factor (TNF) therapy using Certolizumab (Cimzia) for these inflammatory diseases. Studies mostly consist of post hoc analyses. While results may be promising (Ramos et.al. 2021, Gehin et. al. 2019) the retrospective study design limits the ability to obtain data on all outcomes of interest and is only a snapshot in time. Optimal study design should longitudinally evaluate how fluctuations on Certolizumab (Cimzia) may impact disease course. RCTs are needed to assess how measuring ADA improves clinical outcomes. Further research is also needed to develop standardized, clinically validated assays and consensus guidelines for ADA testing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with rheumatoid arthritis, psoriatic arthritis or juvenile idiopathic arthritis and moderate to severe active UC who receive evaluation of serum antibodies related to biologic agents Etanercept (Enbrel) or Simponi/Simponi Aria (Golimumab), the evidence includes systematic review, cohort and observational studies. Relevant outcomes are test validity, change in disease status, health status measures, QOL, and treatment-related morbidity. A systematic review (Strand et. al. 2017) that examined ten biologic agents which included Etanercept (Enbrel) or Simponi/Simponi Aria (Golimumab), ADA rates varied widely among biologics across diseases and are not directly comparable because of immunoassay heterogeneity; the highest overall rates were reported with infliximab (0–83%), adalimumab (0–54%), and

infliximab biosimilar CT-P13 (21–52%), and the lowest with secukinumab (0–1%), ustekinumab (1–11%), etanercept (0–13%), and golimumab (0–19%). ADAb+ versus ADAb- patients had lower rates of clinical response to adalimumab (RA, PsA, JIA, AS, Ps), golimumab (RA), infliximab (RA, PsA, AS, Ps), rituximab (RA), ustekinumab (Ps), and CT-P13 (RA, AS). Higher rates of infusion-related reactions were reported in infliximab- and CTP13-treated ADAb+ patients. While there is evidence that has demonstrated an association between ADA and secondary nonresponse as well as injection-site and infusion-site reactions, the clinical usefulness of measuring ADAs hinges on whether test results inform management changes, thereby leading to improved outcomes, compared with management directed by symptoms, clinical assessment, and standard laboratory evaluation. Limited evidence has described management changes after measuring ADAs. This systematic review found that further research is needed into immunogenicity and the potential benefits of ADAb monitoring, to include clinically validated, standardized ADAb assays to support this management approach. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information

Not applicable.

OBJECTIVE

The objective of this evidence review is to evaluate and compare the net health outcome of 2 types of treatment:

- The first, when serum antibody testing for Infliximab (Remicade), Infliximab Biosimilars (Inflectra, Renflexis, Avsola, Zymfentra), Adalimumab (Humira), Adalimumab biosimilars (Cyltezo), Vedolizumab (Entyvio), Certolizumab (Cimzia), Etanercept (Enbrel), Simponi/Simponi Aria (Golimumab) or Ustekinumab (Stelara), Ustekinumab biosimilars (Pyzchiva, Selarsdi, Stegeyma, Wezlana, Yesinktek) is used in individuals being managed with those drugs.
- The second, when an individual receives standard of care to manage conditions (e.g., rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, inflammatory bowel disease (e.g., moderate to severely active Crohn's disease [CD], ulcerative colitis [UC]) ankylosing spondylitis, and moderate to severe plaque psoriasis associated with the aforementioned drugs.

PRIOR APPROVAL

Not applicable.

POLICY

Measurement of antidrug antibodies in an individual receiving treatment with a biologic agent, either or alone or as a combination test, 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 (Adalimumab Quantitative with Reflex to Antibody Serum Test)
- DoseASSURE™ ADL
- DoseASSURE ™ CTZ
- DoseASSURE ™ ETN

- DoseASSURE ™ GOL
- DoseASSURE ™ IFX
- DoseASSURE ™ UST
- Prometheus® Anser® ADA
- Prometheus® Anser® IFX
- Prometheus® Anser® VDZ
- Prometheus® Anser® UST

POLICY GUIDELINES

NOTE: Iowa House File 2668 (Iowa Code section 514C.36) requires that certain health plans issued or renewed on or after January 1, 2025 “provide coverage for biomarker testing for the purposes of diagnosing, treating, appropriately managing, or monitoring a disease or condition in a covered person when the biomarker testing has demonstrated clinical utility.” Iowa House File 2668 defines clinical utility as ”sufficient medical and scientific evidence indicating that the use of a biomarker test will provide meaningful information that affects treatment decisions and guides improvement of net health outcomes, including an improved quality of life or longer survival.” Wellmark has reviewed this Medical Policy in light of Iowa House File 2668.

Selected U.S. Food and Drug Administration approved biologic agents Adalimumab (Humira), Adalimumab biosimilars (Cyltezo), Certolizumab (Cimzia), Etanercept (Enbrel) Infliximab (Remicade) and Infliximab Biosimilars (Inflectra, Renflexis, Avsola, Zymfentra), Simponi/Simponi Aria (Golimumab), Ustekinumab (Stelara), Ustekinumab biosimilars (Pyzchiva, Selarsdi, Stegeyma, Wezlana, Yesinktek) and Vedolizumab (Entyvio), see Regulatory Status.

Coding

See the Codes table for details.

BACKGROUND

Adalimumab, Certolizumab, Etanercept, Infliximab, Simponi Aria, Ustekinumab and Vedolizumab

Biologic agents (e.g., Infliximab [Remicade], Infliximab biosimilars [Inflectra, Renflexis, Avsola, Zymfentra], Adalimumab [Humira], Adalimumab biosimilars [Cyltezo], Vedolizumab [Entyvio], Simponi/Simponi Aria [Golimumab], Certolizumab [Cimzia], Etanercept [Enbrel] or Ustekinumab [Stelara]), Ustekinumab biosimilars (Pyzchiva, Selarsdi, Stegeyma, Wezlana, Yesinktek) are used to treat multiple inflammatory conditions, including rheumatoid arthritis, moderate to severe psoriatic arthritis, juvenile idiopathic arthritis; inflammatory bowel disease (e.g., moderate to severely active CD or UC), ankylosing spondylitis, and moderate to severe plaque psoriasis (see Wellmark Drug Authorization List). These agents are generally given to individuals who fail conventional medical therapy, and they are typically highly effective for the induction and maintenance of clinical remission. However, not all individuals respond, and a high proportion of individuals lose response over time. It is estimated that 1 in 3 individuals 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 individuals (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 ADA. ADAs are also associated with injection-site reactions and acute infusion reactions and delayed hypersensitivity reactions.

***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: Inflectra, Renflexis, Avsola,* Zymfentra
- *Adalimumab Biosimilars: Cyltezo*
- *Ustekinumab Biosimilars: Pyzchiva, Selarsdi, Stegeyma, Wezlana, Yesinktek*

Detection of Antidrug Antibodies (ADA)

The detection and quantitative measurement of 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 is associated with complexity of the test and prolonged incubation time, along with safety concerns related to the handling of radioactive material. The HMSA assay measures ADA when infliximab is present in serum. Studies evaluating the validation of the results between different assays are lacking, making interstudy comparisons difficult. One retrospective study by Kopylov et.al. (2012) which evaluated 63 individuals 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: (Inflectra, Renflexis, Avsola), Zymfentra); Adalimumab (Humira), Adalimumab biosimilars: (Cyltezo); Vedolizumab (Entyvio), Simponi/Simponi Aria (Golimumab); Certolizumab (Cimzia); Etanercept (Enbrel); or Ustekinumab (Stelara), Ustekinumab biosimilars (Pyzchiva, Selarsdi, Stegeyma, Wezlana, Yesinktek) can be managed in several ways: shortening the interval between doses, increasing the dose, switching to a different biologic agent (in individuals who continue to have loss of response after receiving the increased dose) or switching to a non-biologic agent.

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 ™ CTZ
- DoseASSURE ™ ETN
- 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 (Adalimumab Quantitative with Reflex to Antibody, Serum) test (Mayo Medical Laboratories) 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).

RATIONALE

This evidence review was created in July 2013 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through January 2026.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Measurement of Serum Antibodies to Biologics Agents

Clinical Context and Test Purpose

The purpose of testing serum antibodies to infliximab (Remicade), Infliximab biosimilars: (Inflectra, Renflexis, Avsola, Zymfentra]); Adalimumab (Humira), Adalimumab biosimilars (Cyltezo); Vedolizumab (Entyvio), Simponi/Simponi Aria (Golimumab), Certolizumab (Cimzia), Etanercept (Enbrel), or Ustekinumab (Stelara), Ustekinumab biosimilars (Pyzchiva, Selarsdi, Stegeyma, Wezlana, Yesinktek) in

individuals with arthritis (e.g., rheumatoid, psoriatic, or juvenile idiopathic), inflammatory bowel disease (IBD; moderate or severely active Crohn's disease [CD] or ulcerative colitis [UC]), ankylosing spondylitis, or moderate to severe plaque psoriasis is to improve health outcomes.

The following PICO was used to select literature to inform this review.

Populations

The relevant populations of interest are individuals with arthritis (e.g., rheumatoid, psoriatic, or juvenile idiopathic), IBD (moderate to severely active CD or UC), ankylosing spondylitis, or moderate to severe plaque psoriasis. Both pediatric and adult individuals were considered in this review.

Interventions

The test considered is testing for serum antibodies to Infliximab (Remicade), Infliximab biosimilars: (Inflectra, Renflexis, Avsola, Zymfentra); Adalimumab (Humira), Adalimumab biosimilars (Cyltezo); Vedolizumab (Entyvio); Simponi/Simponi Aria (Golimumab); Certolizumab (Cimzia), Etanercept (Enbrel); or Ustekinumab (Stelara), Ustekinumab biosimilars (Pyzchiva, Selarsdi, Stegeyma, Wezlana, Yesinktek).

Testing may include but are not limited to the following:

- ADALX (Adalimumab Quantitative with Reflex to Antibody, Serum) test (Mayo Medical Laboratories)
- DoseASSURE™ ADL
- DoseASSURE ™ CTZ
- DoseASSURE ™ ETN
- DoseASSURE ™ GOL
- DoseASSURE ™ IFX
- DoseASSURE ™ UST
- Prometheus® Anser® ADA
- Prometheus® Anser® IFX
- Prometheus® Anser® VDZ
- Prometheus® Anser® UST

Comparators

The following practice is currently being used to manage arthritis (e.g., rheumatoid, psoriatic, or juvenile idiopathic), IBD (CD or UC), 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.

Study Selection Criteria

For the evaluation of the clinical validity of this test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Clinically Valid

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

Review of Evidence

Antibodies to Infliximab, Adalimumab, Vedolizumab, and Ustekinumab

There is a substantial body of evidence (numerous systematic reviews and meta-analyses) examining associations between antidrug antibodies (ADA) and nonresponse as well as injection- or infusion-site reactions. Accordingly, this review of the evidence on clinical validity focuses on the most current systematic reviews (see Tables 1 through 3) and studies published after the search dates of those reviews, as well as relevant studies not included in identified reviews (e.g., those focusing on adverse reactions and ADA). In addition, pediatric studies were included in the review, although the majority of data is in the adult population.

Systematic Reviews

Six reviews published from 2012 through 2017 were identified. The number of studies included ranged from 11 to 68, varying by review objectives and conditions of interest. Although not delineated here, there was considerable overlap in selected studies across reviews.

The systematic review and meta-analysis by Pecoraro et al (2017) selected 34 studies (N=4273), including randomized controlled trials (RCTs; n=4), prospective observational (n=22), retrospective observational (n=6), and cross-sectional (n=2). Studies evaluated rheumatoid arthritis (RA; n=18), ulcerative colitis (n=2), Crohn disease (CD; n=5), psoriatic arthritis (n=4), ankylosing spondylitis (n=5), plaque psoriasis (n=4), and spondyloarthritis (SpA; n=1). Most patients (45%) received infliximab, 35% received adalimumab, and 21% received etanercept. None received golimumab or certolizumab. Reviewers identified studies published through August 2016 and rated study quality as good (n=17), fair (n=16), or poor (n=1). The effect of ADA was evaluated in 19 studies, showing a significant ($p<.05$) reduction of response (relative risk [RR]=0.43; 95% confidence interval [CI], 0.3 to 0.63) in ADA-positive patients relative to ADA-negative patients, with adalimumab therapy demonstrating a greater reduction (RR=0.40; 95% CI, 0.25 to 0.65; $p<.001$) than infliximab (RR=0.37; 95% CI, 0.2 to 0.7; $p<.001$). Measures of heterogeneity were 84%, 57%, and 79%, respectively. Fourteen studies reported on the effect of ADA on clinical response (see Table 4). Eleven studies found the risk of developing ADA to be significantly ($p=.03$) lower in patients treated with concomitant methotrexate therapy relative to those treated without methotrexate (RR=0.65; 95% CI, 0.47 to 0.9). Studies comparing treatment response with nonresponse (n=15) found responders to have a significantly ($p<.001$) lower risk of developing ADA relative to nonresponders (RR=0.31; 95% CI, 0.18 to 0.52). The presence of ADA was associated with a significant reduction of tumor necrosis factor (TNF)-α serum concentration (see Table 5). Of the 20 studies (n>2800 patients) reporting data on adverse events, 31% (n=2 studies) developed infections, 18% (n=12 studies) developed injection-site reactions, 8% (n=11 studies) discontinued treatment due to adverse events, and 5% (n=1 study) developed serious adverse events. Although ADA significantly reduced TNF-α response,

the results should be viewed cautiously due to reported study limitations, including small numbers of studies assessed and considerable heterogeneity.

The systematic review and meta-analysis by Thomas et al (2015) included 68 studies (N=14651). Patients had RA (n=8766), SpA (n=1534), or IBD (n=4351). Immunogenicity was examined for infliximab (39 comparisons), adalimumab (15), etanercept (5), golimumab (14), and certolizumab (8). Reviewers identified studies published through December 2013 and included 38 RCTs and 30 observational studies (study quality rated as good [n=32], moderate [n=26], poor [n=10]). The pooled prevalence of ADA varied by disease and drug (see Table 1, highest with infliximab: 25.3%). Duration of exposure (reported in 60 studies) was examined for its potential effect on the development of ADA, and most studies employed enzyme-linked immunosorbent assays (ELISA). The presence of ADA was associated with lower odds of response across most drugs and diseases (see Table 2). An exception was in studies of IBD. Use of immunosuppressive agents substantially decreased the risk of ADA (odds ratio [OR], 0.26; 95% CI, 0.21 to 0.32). Finally, infusion reactions and injection-site reactions were more common (see Table 3) when ADA were detectable (OR=3.25). Evaluation of potential publication bias and overall assessment (e.g., GRADE or similar) for the body of evidence were not reported. Additionally, no measures of heterogeneity were reported.

The systematic review by Meroni et al (2015) searched PubMed through March 2013 and included 57 studies of infliximab (n=34), adalimumab (n=18), and etanercept (n=5). Studies primarily included patients with IBD and RA, but also SpA and psoriasis. Most had prospective cohort designs (n=42), and a formal assessment of study quality (bias) was not reported. Reviewers noted considerable variability in the time from drug administration to ADA and drug bioavailability testing across studies. Various antibody testing assay methods were used and included solid-phases radioimmunoassay (RIA), traditional ELISA, fluid-phase RIA, and bridging ELISA; cutoffs for positive test results were also inconsistently reported. The ranges of patients with detectable ADA varied substantially (see Table 1) but were consistent with other reviews. Qualitatively, the presence of antibodies to infliximab (ATI) was associated with lower levels of infliximab and lower risk of disease control or remission. The presence of antidrug antibody also increased the risk of infusion reactions. When ascertained, the time to development of antidrug antibody varied from as little as 16 weeks to over a year. The time to antibodies to adalimumab (ATA) positivity varied (e.g., 50% of patients with detectable ATA at 28 weeks to a median time of 1 year). Finally, for both infliximab and adalimumab, immunosuppression was associated with less ADA positivity. Reviewers concluded that "…the lack of homogeneity in study design and methodologies used … limited the opportunity to establish the time-course and clinical consequences of anti-drug antibody development...." Although qualitative, reviewers included many studies and provided a detailed review of each not reported by the other meta-analyses.

Nanda et al (2013) conducted a meta-analysis of studies that reported on clinical outcomes according to the presence or absence of ADA in patients with IBD. Several databases were searched to February 2012 (1 was searched to August 2012). Eleven studies involving 707 patients were selected. Six studies (2 RCTs, 1 prospective cohort study, 3 retrospective cohort studies) were included. Selected studies failed at least 1 quality domain (study eligibility criteria, measurement of exposure and outcome, control for confounders, completeness of follow-up), and all studies had a high-risk of bias. The prevalence of detectable ADA in the included studies ranged from 22.4% to 46% (see Table 1). The outcome of interest was a loss of response to infliximab, defined as "relapse of clinical symptoms in patients who were in clinical remission from, or had responded to, infliximab." Measures of loss of response varied across studies and included clinician assessment, standardized scales (Crohn's Disease Activity Index [CDAI], Harvey-Bradshaw Index, Simple Clinical Colitis Activity Index), and the requirement for surgery or presence of a nonhealing fistula. Patients with ATIs had a 3-fold greater risk of loss of response than those without ADAs (RR=3.2; 95% CI, 2.0 to 5.0; shown in Table 2 as the RR of clinical response in treated vs untreated patients to allow comparison with other meta-analyses). This result was influenced

primarily by 532 patients with CD (RR=3.2; 95% CI, 1.9 to 5.5); pooled results for 86 patients with ulcerative colitis were not statistically significant (pooled RR=2.2; 95% CI, 0.5 to 9.0). Eighty-nine patients with unspecified IBD also were included in the meta-analysis. In addition to potential bias in included studies and heterogeneity in outcome assessment, the meta-analysis was limited by variability in the method of ADA detection (double-antigen ELISA, antihuman lambda chain-based ELISA, fluid-phase RIA).

Garces et al (2013) performed a meta-analysis of studies of infliximab and adalimumab used to treat RA, IBD, SpA, and psoriasis. Databases were searched to August 2012, and reviewers selected 12 prospective cohort studies involving 860 patients (540 with RA, 132 with SpA, 130 with IBD, 58 with psoriasis). The outcome of interest was a response, assessed using standard assessment scales for rheumatologic diseases (e.g., European League Against Rheumatism criteria for RA; Assessment in Ankylosing Spondylitis 20% response criteria, or Ankylosing Spondylitis Disease Activity Score for spondyloarthritis; Psoriasis Area and Severity Index for psoriasis) and clinician assessment for IBD. Overall, detectable ADA were associated with a 68% reduction in drug response (pooled RR=0.32). Significant heterogeneity was introduced by varying use of immunosuppressant therapy (e.g., methotrexate) across studies. To assess ADA, most studies used RIA, which is less susceptible than ELISA to drug interference and may be more accurate.

Lee et al (2012) conducted a meta-analysis of patients with IBD receiving infliximab to estimate the prevalence of ADA, the effect of ADA on the prevalence of infusion reactions, and the effect of ADA on disease remission rates. Databases were searched through October 2011, and 18 studies (N=3326) were selected. Studies included RCTs, 5 prospective cohort studies, and 4 retrospective cohort studies. The prevalence of ADA was 45.8% when episodic infusions of infliximab were given and 12.4% when maintenance infliximab was given (see Table 1). Patients with ADAs were less likely to be in clinical remission (see Table 2), but this finding was not statistically significant (RR=0.90; p=.10). Rates of infusion reactions were significantly higher in patients with ADA (RR=2.07; see Table 3). Immunosuppressants resulted in a 50% reduction in the risk of developing ADAs (p<.001). Reviewers concluded that patients with IBD who test positive for ADAs are at an increased risk of infusion reactions but have rates of remission similar to patients who test negative for ADAs.

Table 1. Estimated Prevalence of Antidrug Antibodies from Meta-Analyses

Study	Included Studies	Drugs			Disease			Prevalence of ADA	
		IFX	ADL	Other[a]	IBD	RA	SpA	Pooled (95% CI), %	Range in Studies, %
Lee et al (2012)	18[b]	●			●			20.8 (19.2 to 22.5)	
Episodic	5	●			●			45.8 (41.7 to 50.0)	
Maintenance	10	●			●			12.4 (10.8 to 14.1)	
Nanda et al (2013)	11	●			●				22.4 to 46

Study	Included Studies	Drugs			Disease			Prevalence of ADA	
		IFX	ADL	Other[a]	IBD	RA	SpA	Pooled (95% CI), %	Range in Studies, %
Thomas et al (2015)	39[c]	●			●	●	●	25.3 (19.5 to 32.3)	
	15[c]		●		●	●	●	6.9 (3.4 to 13.5)	
	20	●	●		●			15.8 (9.6 to 24.7)	
	44	●	●	●		●		12.1 (8.1 to 17.6)	
	11	●	●	●			●	8.9 (3.8 to 19.2)	
Meroni et al (2015)	14	●				●			19 to 47
	14	●			●				15 to 61
	5	●					●[d]		26 to 50
	12		●			●			5 to 54
	3		●		●				9 to 46
	3		●				●[d]		18 to 45

ADA: antidrug antibodies; ADL: adalimumab; CI: confidence interval; IBD: inflammatory bowel disease; IFX: infliximab; RA: rheumatoid arthritis; SpA: spondyloarthropathy.
[a] Includes etanercept, golimumab, certolizumab.
[b] Includes 3 studies including both maintenance and episodic therapy.
[c] Number of comparisons in table; did not report studies for pooled prevalence.
[d] Also psoriasis.

Table 2. Results from Meta-Analyses of Antidrug Antibodies and Clinical Response

Study	Included Studies	Drugs			Disease			Clinical Response: ADA vs None		
		IFX	ADL	Other[a]	IBD	RA	SpA	RR (95% CI)	OR (95% CI)	I^2
Lee et al (2012)	18	●			●			0.90 (0.79 to 1.02)		37 %
Nanda et al (2013)	11	●			●			0.33 (0.20 to 0.40)		70 %
Garces et al (2013)	12	●	●		●	●	●[b]	0.32 (0.22 to 0.48)		46 %

Study	Included Studies	Drugs			Disease			Clinical Response: ADA vs None		
		IFX	ADL	Other[a]	IBD	RA	SpA	RR (95% CI)	OR (95% CI)	I^2
Thomas et al (2015)	4	●	●	●	●				1.16 (0.66 to 2.03)	NR
	13	●	●	●		●			0.27 (0.20 to 0.36)	NR
	4	●	●	●			●		0.18 (0.09 to 0.37)	NR
	9	●			●	●	●		0.42 (0.30 to 0.58)	NR

ADA: antidrug antibodies; ADL: adalimumab; CI: confidence interval; I^2: heterogeneity measure; IBD: inflammatory bowel disease; IFX: infliximab; NR: not reported; OR: odds ratio; RA: rheumatoid arthritis; RR: relative risk; SpA: spondyloarthropathy.
[a] Includes etanercept, golimumab, certolizumab.
[b] Also psoriasis.

Table 3. Increased Risk of Adverse Reactions Associated with the Presence of Antidrug Antibodies

Study	Included Studies	Drugs			Disease			Adverse Reactions: ADA vs None	
		IFX	ADL	Other[a]	IBD	RA	SpA	OR (95% CI)	RR (95% CI)
Lee et al (2012)[,]	18	●			●				2.07 (1.61 to 2.67)[a]
Thomas et al (2015)	NR	●	●	●	●	●	●	3.25 (2.35 to 4.51)	

ADA: antidrug antibodies; ADL: adalimumab; CI: confidence interval; IBD: inflammatory bowel disease; IFX: infliximab; NR: not reported; OR: odds ratio; RA: rheumatoid arthritis; RR: relative risk; SpA: spondyloarthropathy.
[a] Infusion reaction.

Table 4. Effect of Antidrug Antibodies on Clinical Response

Outcome Measures	No. Studies	MD	95% CI	I^2, %	p
Disease Activity Score 28	9	0.93	0.41 to 1.44	84	<.001
BASDAI	2	-0.62	-1.51 to 0.27	0	.17
ASDAS	2	0.96	-0.27 to 2.2	0	.13
Psoriasis Area Severity Index	1	4.7	-1.15 to 9.25	NR	.04

Adapted from Pecoraro et al (2017).[,]
ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CI: confidence interval; I^2: heterogeneity measure; MD: mean difference; NR: not reported.

Table 5. Evaluation of Antidrug Antibody Concentration

Outcome Measures	No. of Studies	MD, mg/L	95% CI	I^2, %	p
ADA-positive vs ADA-negative	8	-7.07	-8.9 to -5.25	98	<.001
Responders vs no responders	13	2.77	1.97 to 3.58	82	<.001

Adalimumab therapy	6	5.07	3.77 to 6.36	62	<.001
Infliximab	4	2.74	0.59 to 4.89	62	<.001
Etanercept	3	0.85	0.41 to 1.13	82	<.001
DAS28 change from baseline	8	-2.18	-2.91 to -1.44	97	<.001

Adapted from Pecoraro et al (2017).
ADA: antidrug antibodies; CI: confidence interval; DAS28: Disease Activity Score in 28 joints; I^2: heterogeneity measure; MD: mean difference.

Cohort Studies

This review identified several publications not included in a systematic review. The results of the most recent publications are consistent with the conclusions of the systematic reviews.

Bouden et al (2024) reported on a cross-sectional, multi-center study (N=197) evaluating infliximab and adalimumab ADA, and their impact on therapeutic response in patients with rheumatoid arthritis (RA), spondyloarthritis (SpA), or Crohn disease (CD) who were treated with either drug for at least 6 months. The presence of ADA was detected in 40% of patients treated with infliximab and 25% with adalimumab, with the highest prevalence in SpA (40%), followed by RA (35%) and CD (21%). A statistically significant inverse correlation was observed between levels of ADA and trough levels of infliximab and adalimumab across all conditions; however, the presence of ADA was not associated with disease activity. Concomitant methotrexate use significantly reduced immunogenicity.

Cludts et al (2017) conducted a single-center retrospective cohort analysis of patients with RA (n=18), psoriatic arthritis (n=9), or ankylosing spondylitis (n=12) in Italy. Serum samples were taken prior to adalimumab therapy and after 12 and 24 weeks of treatment. Psoriatic arthritis and ankylosing spondylitis patients were grouped together due to axial involvement in all psoriatic arthritis patients. Although adalimumab levels varied among patients (0 to 30 mg/mL), median levels were significantly lower at 12 and 24 weeks in ATA-positive samples, and antibody formation was associated with decreasing levels of circulating adalimumab. A reporter gene assay detected neutralizing antibodies against TNF antagonists in ATA-positive, therapeutic-negative patients; however, neutralization could not be confirmed in all ATA-positive samples due to adalimumab interference. There was a negative correlation between ATA levels and adalimumab in all groups, with 43.6% and 41% of the adalimumab-treated patients developing antibodies at 12 and 24 weeks, respectively. These percentages increased to 48.7% and 46% after subjecting the samples to acid treatment. There was a negative correlation between adalimumab trough levels and Disease Activity Score in 28 joints (DAS28) and Bath Ankylosing Spondylitis Disease Activity Index scores (p<.001). There were no significant differences in Bath Ankylosing Spondylitis Disease Activity Index scores between ATA-positive and ATA-negative patients at 12 or 24 weeks. Study findings are consistent with others, suggesting that adalimumab levels 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.

Using an observational, cross-sectional study design, Ara-Martin et al (2017) analyzed the impact of immunogenicity on response to anti-TNF therapy in 137 adults with moderate-to-severe plaque psoriasis at 35 centers in Spain between 2012 and 2014.[1] All patients experienced secondary nonresponse to adalimumab (n=65), etanercept (n=47), and infliximab (n=19) after 6 or more months of treatment. Serum ADA was identified in 48%, 0%, and 42% of patients treated with adalimumab, etanercept, and infliximab, respectively. Loss of efficacy was assessed using the Psoriasis Area and Severity Index (PASI; >5), 75% improvement in PASI score from baseline (PASI75), and/or the Physician Global Assessment (>2). Physician Global Assessment values for ADA-positive versus ADA-negative patients were significantly worse in the adalimumab group (3.7 vs 3.2; p=.02) but not in the infliximab group. There was a significant

negative linear correlation between serum drug concentrations and ADA in the adalimumab group (p=.001) and among the 3 groups combined (p=.001), and a significant (p=.019) correlation between serum ADA titer and body surface area. Unlike the other studies, in this study, the use of concomitant antirheumatic drugs was not associated with anti-TNF immunogenicity in any of the groups. This study provided evidence of antibody development against adalimumab and infliximab (not against etanercept) in patients with psoriasis, with ADA formation accounting for half of the secondary nonresponse associated with these therapies. However, conclusions were limited due to the cross-sectional study design, the use of ELISA to detect ADAs due to drug interference, the potential presence of neutralizing antibodies as confounding factors, and limited information about patients' health status prior to the study period.

A case-control, longitudinal study by Lombardi et al (2016) evaluated possible confounding factors by analyzing adalimumab treatment for psoriasis in 5 distinct groups, including individuals who received: biologic therapies after switching from adalimumab (n=20); ongoing adalimumab therapy (n=30); novel adalimumab therapy (n=30); biologic therapies other than adalimumab (n=15); and no treatment with immunosuppressants or biologics (n=15), serving as a quasi-control. The clinical severity of psoriasis was scored using the PASI. At a 12-month follow-up, ADA was highest (87%) in patients who received biologic therapies after switching from adalimumab. The false-positive rate was 23% for adalimumab detection and 22% for anti-adalimumab antibodies in individuals who were never treated with adalimumab. There were no significant differences in median PASI scores between the anti-adalimumab antibody-negative patients (1.1) and the anti-adalimumab antibody-positive patients (4.0). There was no association between PASI score or TNF-α concentration and the presence of anti-adalimumab antibodies in patients receiving adalimumab. Additionally, there were no significant differences in TNF-α and C-reactive protein concentrations. Study limitations included the observational design, small sample size, use of ELISA to measure ADA, and high variability of results. The authors concluded that the assay has limited clinical utility.

Arstikyte et al (2015) prospectively evaluated the association between ADA and adverse events, clinical response, and serum drug levels in 143 symptomatic patients (62 with RA, 81 with SpA; mean age, 45 years) treated with TNF blockers in Lithuania. All patients receiving adalimumab or infliximab were tested and 1 in 3 patients was given etanercept (because it is more commonly used). A response in RA patients was defined as either good, moderate, or low using European League Against Rheumatism criteria[14,]; SpA disease activity was considered inactive, moderate, high, or very high by established criteria,[15,] with inactive and moderately active disease defined as a response. At least 3 months after therapy initiation, a single serum sample was obtained prior to dosing between 2012 and 2013; disease activity and other patient characteristics (e.g., symptom duration, health status) were assessed concurrently. Serum adalimumab, infliximab, and etanercept levels were obtained; ADA was assayed using a bridging ELISA. Of 57 patients receiving infliximab, 14 (24.6%) had detectable antibodies, with 13 of the 14 undetectable infliximab trough levels. Disease activity at baseline was unassociated with the development of ADA in either disease. In patients achieving a response, infliximab and adalimumab trough levels were higher, but not significantly (p=.09 and p=.14, respectively). However, adalimumab concentrations were significantly higher in nonresponders (p<.001). ATI were associated with infusion reactions but with little certainty (OR=5.9; 95% CI, 1.0 to 33.3) as was stopping infliximab treatment or changing agent. Study strengths included its prospective design, standardized assessments, and responder definition. Limitations were the small number of nonresponders and lack of specificity on whether any eligible participants declined enrollment.

Jani et al (2015) measured ADA and RIA together, with drug levels in 331 RA patients treated with adalimumab (n=160) or etanercept (n=171) between 2008 and 2013. Patients were participants in the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate, conducted in 60 centers across the United Kingdom. Disease activity was assessed using the DAS28. The response was

evaluated using European League Against Rheumatism response criteria or change in the DAS28 score. Following 12 months of adalimumab therapy, ADA were detectable in 24.8% of patients (almost all were detectable by 6 months) and were associated with lower serum drug levels. Both routine (nontrough) drug levels and ATA were associated with DAS28 scores at 12 months. In predicting European League Against Rheumatism nonresponse, the area under the curve for an adalimumab concentration less than 5 mg/mL at 3 months was 0.66 (95% CI, 0.55 to 0.77) and 0.68 (95% CI, 0.54 to 0.81) for the presence of ADA. None of the etanercept patients developed detectable ADA. Although derived from a well-established observational study designed 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.

Frederiksen et al (2014) conducted a single-center retrospective cohort study of IBD patients treated with infliximab (n=187) or adalimumab (n=57) in Denmark. ADA were assayed using fluid-phase RIA; 49% of infliximab-treated patients developed antibodies compared with 21% of those treated with adalimumab. Development of ATA was associated with secondary nonresponse: the positive predictive value was 91% (95% CI, 59% to 100%), sensitivity was 50% (95% CI, 27% to 73%); the negative predictive value was 74% (95% CI, 57% to 87%), and specificity was 97% (95% CI, 82% to 100%) (values varied by adalimumab trough levels). The authors also 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 evaluations of ADA using RIA (a strength of this study). Conclusions were limited by the retrospective design and sample size.

While many studies have evaluated the clinical validity using single ADA measurements, at least 1 assessed their persistence over time. Vande Casteele et al (2013) analyzed infliximab trough and ATI levels using a homogeneous mobility shift assay with banked serum obtained from 90 IBD patients treated between 1999 and 2011. ATI levels had been previously assayed using an ELISA-based test. A total of 1232 samples were evaluated (mean, 14 per patient). Treatment decisions were made solely on clinical evaluation and C-reactive protein levels. ATI were detected in 53 (59%) of 90 patients but subsequently were nondetectable in 15 (28%) of the 53. Persistent ATIs were associated with discontinuation of infliximab (RR=5.1; 95% CI, 1.4 to 19.0), but the wide CI reflects considerable uncertainty.

Chanchlani et al (2023) investigated factors predicting anti-TNF treatment failure and strategies to prevent or mitigate loss of response as part of a multicenter, prospective observational cohort study (Personalised Anti-TNF Therapy in Crohn's Disease (CD) [PANTS]). This study reported on the effectiveness of infliximab and adalimumab in anti-TNF-naive patients ≥6 years of age with active luminal CD. An extension of this study, PANTS-E, included 598 patients, of whom 389 were treated with infliximab and 209 were treated with adalimumab. In PANTS-E, by the end of year 3, the estimated proportion of patients who developed ADA associated with undetectable drug concentrations was 44.0% in those treated with infliximab, and 20.3% in those treated with adalimumab. The development of ADA with undetectable drug levels was significantly associated with treatment without concomitant immunomodulator use in both groups (hazard ratio [HR] for immunomodulator use: infliximab, 0.40 [95% CI, 0.31 to 0.52]; adalimumab, 0.42 [95% CI, 0.24 to 0.75]). Additionally, the presence of ADA at week 14 correlated with lower remission rates at year 2 (infliximab: OR=0.44 [95% CI, 0.21 to 0.81]; adalimumab: OR=0.16 [95% CI, 0.00 to 0.46]) and year 3 (infliximab: OR=0.37 [95% CI, 0.15 to 0.72]; adalimumab: OR=0.21 [95% CI, 0.08 to 0.71]). Finally, among the 522 infliximab-treated patients with a positive test for ADA at any time point, 442 (85%) were re-tested at least 4 weeks later. Of these, 76 (17%) had negative repeat tests, while 366 (83%) remained positive. The median concentration of ADA at the initial test was 11.0 AU/mL (interquartile range [IQR], 9.0 to 17.3) in those who later tested negative, compared to 18.0 AU/mL (IQR, 12.0 to 34.0) in those who remained positive. For the 191 adalimumab-treated patients with a positive test for ADA, 126 (66%) were re-tested at least 4 weeks later. Of these, 34 (27%) had negative

repeat tests, while 92 (73%) remained positive. The median ADA concentration at the initial test was 8.4 AU/mL (IQR, 6.0 to 15.0) in those who later tested negative, compared to 15.0 AU/mL (IQR, 7.0 to 54.0) in those who remained positive. Although the transience of ATI in IBD has not been carefully scrutinized, findings by Casteele et al (2013) and Chanchlani et al (2023) suggest that caution is needed when interpreting a single ATI result.

Zitomersky et al (2023) reported on a single center prospective cohort study of 218 children and young adults with inflammatory bowel disease (IBD) receiving infliximab with over 3 years of follow-up. On average, each patient had 4 samples assessed for infliximab levels and ATI (919 total samples). A total of 60 patients were found to have ATI, 22 of whom discontinued infliximab. In total, 14 of 31 patients who discontinued infliximab had detectable ATI at study onset. The combination of ATI and subtherapeutic infliximab level (<0.5 µg/mL) at study entry was associated with the highest risk of drug discontinuation (ATI: HR=4.27 [p<.001]; subtherapeutic infliximab level: HR=3.2 [p=.001]). Infliximab dose escalation eliminated ATI in 21 of 60 patients.

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 individuals receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

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

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

Syversen et al (2021) reported on the results of a randomized, parallel-group, open-label trial of 411 adults with rheumatoid arthritis (RA), spondyloarthritis (SpA), psoriatic arthritis, ulcerative colitis, Chron's disease (CD), or psoriasis who received either proactive therapeutic drug monitoring of infliximab therapy based on serum infliximab level and ADA, or standard therapy without serum infliximab level or ADA. Serum trough infliximab levels and ADA were measured at each infusion in the therapeutic drug monitoring group. The infliximab dose or interval could be adjusted based on the therapeutic range during induction and during treatment. If ADA was greater than 50 mcg/L at any point, therapy with infliximab was switched to a different agent.

There was no difference between the therapeutic drug monitoring group and standard therapy group in clinical remission at week 30 (50.5% vs 53% of patients, respectively; p=.78). During infliximab treatment, 36 (18%) patients in the therapeutic drug monitoring group and 34 (17%) in the standard therapy group developed ADAs ≥15 mcg/L. Antidrug antibodies ≥50 mcg/L (the threshold for discontinuation) occurred in 20 (10%) patients in the therapeutic drug monitoring group and 30 (15%) in the standard therapy group. The remission rate in patients who developed ADAs was 56% in the therapeutic drug monitoring group

and 35% in the standard therapy groups. The trial was limited by the small sample size of subjects who developed ADAs.

Steenholdt et al (2014) reported on the results of a noninferiority trial and cost-effectiveness analysis of 69 patients with Chron's disease (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. Patients with subtherapeutic infliximab level (<0.5 µg/mL) had the 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 in a single-blind fashion (patients were unaware, but investigators were aware of the 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 arm, included bile acid malabsorption, strictures, and irritable bowel syndrome. In both intention-to-treat 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 score for patients with nonfistulizing disease and a minimum 50% reduction in active fistulas for patients with fistulizing disease (intention-to-treat, 58% in the algorithm group vs 53% in the control group; p=.810; per-protocol, 47% in the algorithm group vs 53% in the control group; p=.781). Only the intention-to-treat analysis fell within the prespecified noninferiority margin of -25% for the difference between groups.

Conclusions on the noninferiority of an algorithmic approach compared with dose intensification from this trial are limited. The noninferiority margin was arguably large and was exceeded in the conservative per-protocol analysis. Dropouts were frequent and the 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 ulcerative colitis) with clinical relapse (CDAI score >220 or Mayo Clinic score >5) during treatment with adalimumab 40 mg every 2 weeks. For all patients, trough adalimumab levels and ADA were measured in a blinded fashion using ELISA, and adalimumab doses were optimized to 40 mg weekly. Those who did not achieve clinical remission (CDAI score <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/mL), (2) those with a subtherapeutic adalimumab level and undetectable ATA; and (3) those with a subtherapeutic 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<.01 vs group 2) and group 3 (2 [12%] of 17 patients; p<.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<.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<.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 ulcerative colitis) 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<.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<.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<.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 IBD who relapse on adalimumab and have subtherapeutic serum adalimumab levels may benefit from a higher adalimumab dose if ATA is undetectable or from a change to another TNF inhibitor if ATA is detectable. Relapsed patients who have therapeutic serum adalimumab levels may benefit from change to a different drug class. The strengths of the study included 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 levels for decision making. A subsequent study comparing the management using the algorithm proposed with usual care is needed. Finally, the lead author of the study received lecture fees from the ADA test provider (Theradiag).

Afif et al (2010) evaluated the clinical utility of measuring ATI (referred to as human antichimeric antibodies in the study) and infliximab concentrations by retrospectively reviewing patient medical records. Record review from 2003 to 2008 identified 155 patients who had had ATI, had data on infliximab concentrations and met the study inclusion criteria. A single physician ordered 72% of the initial tests. The authors retrospectively determined clinical response to infliximab. Forty-seven percent of patients were on concurrent immunosuppressive medication. The main indications for testing were a loss of response to infliximab (49%), partial response after initiation of infliximab (22%), and possible autoimmune or delayed hypersensitivity reaction (10%). ATI were identified in 35 (23%) patients and therapeutic infliximab concentrations in 51 (33%) patients. Of 177 tests assessed, the results impacted treatment decisions in 73%. In ATI-positive patients, change to another anti-TNF agent was associated with a complete or partial response in 92% of patients, whereas dose escalation occurred in 17%.

The authors concluded that the measurement of ATI and infliximab concentration had a clinically useful effect on patient management. The strategy of increasing infliximab dose in patients with ATI was ineffective, whereas in patients with subtherapeutic infliximab concentrations, this strategy was a good alternative to changing to another anti-TNF agent. Study limitations included the retrospective design and use of ELISA testing for ATI. Because there was no control group, it cannot be determined what changes in management would have been made absent ATI measurement. Because clinicians are likely to change management for patients who do not achieve or maintain a clinical response, it is important to understand how these management decisions differ when ATI is measured.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of testing anti-TNF-α inhibitor antidrug antibody or ATA in this population has not been established, a chain of evidence supporting clinical utility cannot be constructed.

Section Summary: Antibodies to Infliximab, Adalimumab, Vedolizumab, and Ustekinumab

A large body of evidence has evaluated the clinical validity of ADA testing. ADA has been associated with secondary nonresponse in RA, SpA, and possibly IBD. The presence of ADA has been consistently associated with an increased risk of an infusion-site reaction related to infliximab and injection-site reactions related to adalimumab. A concomitantly administered immunosuppressant agent may reduce the risk of developing ADA. Although ADA significantly reduced TNF-α response in a recent meta-analysis, considerable heterogeneity limits those findings. In addition, an observational study found no association between concomitant immunosuppressants and anti-TNF immunogenicity in patients with psoriasis. A second cohort study found no association between PASI score or TNF-α concentration and the presence of anti-adalimumab antibodies in patients receiving adalimumab to treat psoriasis. A third cohort study found a statistically significant inverse correlation between levels of ADA and trough levels of infliximab and adalimumab in individuals with RA, SpA, and CD, but ADA presence did not correlate with disease activity.

Convincing evidence for the clinical utility of ADA testing is currently lacking. An RCT did not find a difference in relapse rates with therapeutic drug monitoring of infliximab using trough levels and ADA compared to standard therapy without monitoring these levels. Uncontrolled retrospective studies in IBD have demonstrated the impact of ADA testing on treatment decisions but cannot demonstrate improved patient outcomes compared with a no-testing strategy. Additional limitations of these studies included a lack of clinical follow-up after treatment decisions were made and a lack of clinical assessments to guide treatment decisions. Additionally, the determination of a clinically relevant threshold for the ADA level is complicated by the use of various assay methods. A small, nonrandomized prospective study suggested that ADA levels may be informative in relapsed patients with IBD who have low serum adalimumab levels, but this finding requires confirmation in larger, randomized trials. Methodologic flaws, including relapse misclassification, limit conclusions from the RCT in patients with relapsed IBD. Direct or indirect evidence for clinical utility in patients with RA or SpA was not identified. Finally, although ADA is associated with increased risk of infliximab infusion- and adalimumab injection-site reactions, whether testing for ADA can reduce that risk is unclear. For example, the Lichtenstein (2013) systematic review of infliximab-related infusion reactions concluded: “…there is a paucity of systematic and controlled data on the risk, prevention, and management of infusion reactions to infliximab.”

Antibodies to Certolizumab, Etanercept, and Simponi/Simponi Aria

Review of Evidence

Certolizumab (Cimzia)

Case Studies

Ramos et. al. (2021) in a single-center (Mayo Clinic in Rochester, MN) retrospective evaluation (between October 2016 and October 2019) assessed a combination testing approach using certolizumab pegol (CZP) trough levels and antibodies (ADA) in Crohn disease (CD) on maintenance CZP. Primary outcomes included median CZP trough levels (CTL) in the cohort and presence of anti-CZP ADA. Secondary outcomes were based on median CTL associated with: biochemical response (BR), defined as CRP <8 mg/dL; radiologic response (RR), defined as improvement per radiology impression on CT enterography and/or MR enterography; RH, defined as absence of inflammation on CT enterography and/or MR enterography imaging; clinical response (CR), defined as improvement in reported symptoms; and MH, defined as absence of mucosal ulcers in CD. Deep remission (DR) was defined as achieving both MH and CR. Seventy-seven patients were included whom completed induction with CZP and received

maintenance dosing of either 400 mg subcutaneously every 4 weeks (n=44) or 200 mg every 2 weeks (n=33). The overall median CTL was 18.9 ug/mL (interquartile range, 7.6-35.4). In patients receiving CZP every 2 weeks the median level was 28.7 vs 13.4 ug/mL in every 4 weeks (p = 0.12). Biochemical response data was available in 57 patients (65%) and clinical outcomes are summarized in Table 6. In this study the use of therapeutic drug monitoring (TDM) in clinical practice among patients with CD treated with CZP, the median CTL was 18.9 ug/mL, and 27.3% of patients had anti-CZP antibodies. These results demonstrated that higher CTL was significantly associated with CR and RR and lower CTL resulted in changed in clinical management in 61% of cases, with the presence of anti-CZP antibodies increasing the odds (OR, 5.6) of changes occurring. While patients receiving CZP dosing at least every 2 weeks had higher odds of achieving MH, the presence of anti-CZP antibodies negatively impacted the odds of achieving CR and RR. Study limitations included sample size, restriction to a single referral center preventing broader analysis of factors capable of interfering with CTL, and the retrospective design limited the ability to obtain data on all outcomes of interest. The authors concluded “while the presence of ADA is frequent and associated with poorer outcomes, higher CTL directly correlate with CR, RR, RH and MH. CTL of at least 19 ug/mL should be sought in order to optimize outcomes in clinical practice. Further studies should focus on assessing prospectively how changes on TDM reflect different disease activity states. Lastly, exploring mechanisms leading to the development of ADA, not restricted to CZP, could reveal new strategies to optimize drug levels and consequently, improve clinical outcomes.”

Table 6. CTLs and Clinical Outcomes

	Entire Cohort (n = 77)
CZP levels, ug/mL	19.9 (7.6-35.4)
Positive CZP antibody	21 (27.3%)
CRP, mg/L	8.9 (3.5-22.4)*
MH on endoscopy	20/51 (39.2%)
RH	14/46 (30.4%)
RR	11/45 (48.9%)
CR	39/77 (50.6%)
DR	15/51 (29.4%)
Change in management based on level	47 (61.0%)
• Increased dose • IMM added • Drug discontinued	18 (23.4%) 2 (2.6%) 27 (35.0%)

MH, mucosal healing; RH, radiologic healing; RR, radiologic response; CR, clinical response; CZP, certolizumab pegol; CTL, certolizumab trough level; IMM, immunomodulator; DR, deep remission; Data are given as n (%) or median (interquartile ranges). *CRP data Were available in 57 patients.

Gehin et. al. (2019) in a retrospective review evaluated the association between certolizumab pegol (CZP) serum levels, anti-drug antibodies (ADAb) and treatment response in patients with inflammatory joint disease (IJD) using data from the NOR-DMARD study from January 2013 to December 2016 (n= 310; 116 axial spondylarthritis [axSpA], 91 rheumatoid arthritis [RA], 61 psoriatic arthritis [PsA] and other IJD 42). The NOR-DMARD registry is a longitudinal observational study including adult patients with IJD starting treatment with biologic-disease modifying antirheumatic drugs (bDMARDs). CZP serum drug and anti-drug antibody levels were measured in serum samples collected after 3 - and 6- month follow-up visits using automated in-house assays. Disease activity was assessed by utilizing Ankylosing Spondylitis Disease Activity Score-C-reactive protein (ASDAS-CRP) for axSpA and Joint Disease Activity Score-Erythrocyte Sedimentation Rate (DAS28-ESR) for RA and PsA. Treatment response was defined by ASDAS Clinically important improvement (CII) (defined by a reduction of ≥ 1.1 units in ASDAS-CRP) in axSpA, and the European League Against Rheumatism (EULAR) good/moderate response in RA and DAS28 improvement ≥ 0.6 in PsA. Patients with axSpA, RA and PsA with available baseline disease

activity score were included in response analyses (*n* = 245; 110 axSpA, 81 RA, 54 PsA) (Table 6). Having a serum CZP level ≥ 20 mg/L was associated with response at 3 and 6 months for all three diagnoses combined (OR 2.3 (95% CI 1.2–4.5, *P* = 0.01), OR 1.9 (95% CI 1.0–3.5, *P* = 0.05), respectively). However, CZP levels ≥ 40 mg/L were not associated with any additional benefit, and response rates were, on the contrary, lower across all diagnoses. Considerable inter-individual variation in serum CZP concentrations on the same standard dose was revealed, suggesting both over- and undertreatment. Disease activity measures and response criteria are defined differently in axSpA, RA and PsA, which could affect interpretation and comparability of results. The relatively short time from patients receiving the standard loading dose to the collection of biobank samples in the study, some of the patients may not have reached steady-state drug levels. In total, ADAb against CZP was detected in 6.1% of patients after 3 months of treatment and they found early development of ADAb was associated with low drug levels and reduced treatment response. The data was not able to demonstrate a protective effect of concomitant synthetic DMARDs on ADAb formation in RA patients and the number of ADAb-positive RA patients was too small to conclude. Studies assessing ADAb frequency are not necessarily comparable, because of differences in patient selection, study design and methods used to measure ADAb. The authors concluded "establishment of a therapeutic target interval is necessary for further validation of therapeutic drug monitoring (TMD) in patients on CZP treatment. Our results demonstrate that CZP serum levels vary considerably between patients with IJD on standard dose. Serum levels ≥ 20 mg/L were associated with treatment response. However, having CZP level > 40 mg/L was not associated with any additional benefit. Results were comparable between diagnoses. ADAb against CZP were associated with low drug levels and reduced treatment response. These results suggest that a therapeutic interval of 20–40 mg/L can be implemented in clinical practice for non-trough serum samples in patients with IJD, but the clinical significance of tailoring tumor necrosis factor-α inhibitors (TNFi) treatment in IJD by TDM should be further explored in randomized controlled clinical (RCT) strategy trials."

Section Summary: Certolizumab (Cimzia)

There is currently paucity of evidence in the published peer reviewed medical literature evaluating the effectiveness of testing strategies including evaluation for serum to Certolizumab (Cimzia) in individuals with Crohn's disease, rheumatoid arthritis, psoriatic arthritis and plaque psoriasis. Studies mostly consist of post hoc analyses. While results may be promising (Ramos et.al. 2021, Gehin et. al. 2019) the retrospective study design limits the ability to obtain data on all outcomes of interest and is only a snapshot in time. Optimal study design should assess whether measuring ADA improves clinical outcomes. Further research is also needed to develop standardized, clinically validated assays and consensus guidelines for ADA testing.

Etanercept (Enbrel)

Systematic Review

Strand et. al. (2017) conducted a systematic review to examine the immunogenicity of ten biologic agents and one approved biosimilar agent (abatacept, adalimumab (ADA), CT-P13 INF biosimilar, certolizumab pegol, etanercept (ENT), golimumab (GLM), infliximab (INF), rituximab (RTX), secukinumab (SEC), tocilizumab and ustekinumab (UST) across inflammatory diseases (rheumatoid arthritis (RA), psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis, psoriasis (Ps), Crohn's disease and ulcerative colitis). The focus of this study was on the reported frequency of anti-drug antibodies (ADAb) formation; potential effects of ADAb on pharmacokinetics, efficacy and safety. A total of 443 publications (394 studies) were included in this review. The ratio of RCTs to non-RCTs and observational studies varied widely among the biologic/biosimilar agents. Anti-drug antibody (ADAb) rates varied widely among biologics across diseases and are not directly comparable because of immunoassay

heterogeneity; the highest overall rates were reported with infliximab (0–83%), adalimumab (0–54%), and infliximab biosimilar CT-P13 (21–52%), and the lowest with secukinumab (0–1%), ustekinumab (1–11%), etanercept (0–13%), and golimumab (0–19%). Most ADAbs were neutralizing, except those to abatacept and etanercept. ADAb+ versus ADAb- patients had lower rates of clinical response to adalimumab (RA, PsA, JIA, AS, Ps), golimumab (RA), infliximab (RA, PsA, AS, Ps), rituximab (RA), ustekinumab (Ps), and CT-P13 (RA, AS). Higher rates of infusion-related reactions were reported in infliximab- and CTP13-treated ADAb+ patients. Background immunosuppressives/anti-proliferatives reduced biologic immunogenicity across diseases. The authors concluded "In the published literature, ADAb positivity has been consistently linked to diminished clinical improvement and loss of response with several biologic/biosimilar agents, including ADA, GLM, INF, RTX, and CT-P13, but direct causation has not been established and other processes may play a role." Further research is needed into immunogenicity and the potential benefits of ADAb monitoring, to include clinically validated, standardized ADAb assays to support this management approach.

Cohort Study

Bitoun et. al. (2023) in a prospective cohort study evaluated the association between the presence of ADA and response to biologic disease – modifying antirheumatic drugs, including adalimumab, infliximab, etanercept, tocilizumab, and rituximab, in adults 18 years or older with rheumatoid arthritis (RA) from 27 recruiting centers in 4 European countries (France, Italy, the Netherlands, and the UK) that were initiating a new bDMARD between March 2014 to June 2016 with study completion in 2018 and data analysis completed in June 2022. "The primary outcome was the association of antidrug antibody positivity with EULAR (European Alliance of Associations for Rheumatology; formerly, European League Against Rheumatism) response to treatment at month 12 assessed through univariate logistic regression. The secondary end points were the EULAR response at month 6 and at visits from month 6 to months 15 to 18 using generalized estimating equation (GEE) models. Detection of antidrug antibody serum levels was performed at months 1, 3, 6, 12, and 15 to 18 using electrochemiluminescence (MSD; Meso Scale Discovery) and drug concentration for anti-TNF mAbs, and etanercept in the serum was measured using enzyme-linked immunosorbent assay." Two hundred thirty (230) patients were included in the analysis which included 117 females (77.0%) and 53 males (23.0%) with mean age of 54.3 years. Patients with anti-TNF mABs n=68, patients treated with etanercept n=82, patients treated with rituximab n=30 and patients treated with tocilizumab n=50. Antidrug antibodies were present within 12 months in 26 of 68 patients (38.2%) who were treated with anti-TNF mAbs, 5 of 82 patients (6.1%) who were treated with etanercept, 10 of 50 patients (20.0%) who were treated with tocilizumab, and 15 of 30 patients (50.0%) who were treated with rituximab. There was an inverse association between antidrug antibody positivity and EULAR response at month 12 for all bDMARDs (OR, 01.9 [95% CI, 0.09-0.38]; p < .001). Analyzing all visits starting at month 6 and including months 12, 15 to 18 using generalized estimating equation (GEE) found the antidrug antibody positivity status for all bDMARDs inversely associated with response to treatment (OR, 0.41; 95% CI, 0.20-0.83); p = .01). There was a significantly higher drug concentration of anti-TNF mAbs in patients with antidrug antibody – negative vs antidrug antibody – positive status (mean difference, −9.6 [95% CI, −12.4 to −6.9] mg/L; P < .001). Etanercept drug concentration at 1 month (mean difference, 0.70 [95% CI, 0.2-1.2] mg/L; p = .005) which was the only time point of patients with transient-positive status was significantly lower in the 6 patients with transient antidrug antibodies compared with the others. Methotrexate comedication in 165 patients (71.7%) at bDMARD therapy initiation at baseline was inversely associated with antidrug antibodies (OR, 0.50; 95% CI, 0.25-1.00; P = .05). Limitations associated with this study include the following:

- Demonstrated an association when all biologic agents were analyzed together, however, the study was not powered to demonstrate an association for each drug class.

- There was a substantial proportion of patients in the unclassified category, these patients were defined as strictly missing 1 or more antidrug antibody measurements for the analysis of response at month 12.
- The antidrug antibodies were not the only factors that were independently inversely associated with response to treatment in the GEE analysis.
- The MSD technique used is not widely available to clinicians, but the authors state “the percentage of immunized patients in this study is within the same range observed in other studies using the available classical sandwich ELISA technique.”
- The secondary endpoints were not corrected for multiple tests and should be considered exploratory.

The authors concluded based on this study that of patients with RA, “response to biologic drugs was inversely associated with antidrug antibody positivity and monitoring of antidrug antibodies could be considered in the personalized management of patients with RA, particularly nonresponders.”

Simponi and Simponi Aria (Golimumab)

Systematic Review

See the systematic review above Strand et. al. (2017) which includes golimumab in the treatment inflammatory diseases (rheumatoid arthritis (RA), psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis, psoriasis (Ps), Crohn’s disease and ulcerative colitis), which focused on the reported frequency of anti-drug antibodies (ADAb) formation; potential effects of ADAb on pharmacokinetics, efficacy and safety.

Observational Studies

Tawa et. al. (2022) in a prospective observational study in adult patients (n = 26) with ulcerative colitis (UC) evaluated whether serum measuring ABAs in combination with serum golimumab (GLM) trough levels (TLs), early after initiation of induction therapy affected the long-term outcomes in UC and identify clinically relevant TLs that should be targeted for better long-term outcomes. The primary outcome was clinical remission at 54 weeks and was measured by serum GLM TLs at week 6, 10 and 14. Clinical response was defined as a decrease from baseline score by at least three points, and 30% decrease in pMayo score, accompanied by a decrease of at least one point in the rectal bleeding score, or a rectal bleeding score of zero. Clinical and laboratory remission was defined as being in clinical remission with a normal C-reactive protein level. GML TLs were determined using Golimumab ELISA and Anti-GML antibodies were determined using the qualitative Antibody to Golimumab ELISA Kit. Anti-GLM antibody status (detectable or not detectable) could only be reported qualitatively. This assay did not allow for the detection of antidrug antibodies in the presence of GLM. Anti-GLM antibodies were evaluated in serum samples obtained at week 14. Serum GLM TLs at weeks 6, 10, and 14 were compared between patients in clinical remission and nonremission at week 54. GLM TLs were not associated with clinical remission at week 6 and week 10. However, the serum GLM TLs at week 14 were associated with clinical remission at 54 weeks of treatment (median [IQR] 1.6 [1.3–1.6] µg/mL vs. 0.9 [0.6–1.3] µg/mL, $p = 0.043$). Also, the GLM TLs at week were higher in clinical response patients at week 54, than those who were not in response (median [IQR] 1.6 [1.4–1.8] µg/mL vs. 0.8 [0.6–1.0] µg/mL, $p = 0.009$). At week 14, three patients (11.5%) had detectable anti-GML antibodies. There was no difference in the positive detection of anti-GLM antibodies between patients in remission and nonremission at week 14 (1 [9.1%] out of the 11 patients vs. 2 [13.3%] out of 15 patients, $p = 0.738$). Also, there was not a significant different in the positive detection of anti-GLM antibodies at week 14 between remission and nonremission patients at

week 54 (1 [12.5%] out of 8 patients vs. 2 [11.1%] out of the 18 patients, $p = 0.574$). These results are consistent suggesting that immunogenicity assessing anti-GLM antibodies may not play a role in GLM efficacy. Limitations of this study include small sample size, endoscopic remission was not the primary endpoint, therefore, based on GLM outcomes at week 54 may have appeared to improve, and while the assays utilized for GLM TLs and anti-GLM antibodies were commercially available, however, caution should be exercised when comparing target thresholds between studies as the measurements cannot be directly compared if different assays were utilized to obtain these measurements. The authors conclude "further studies are needed to assess the value of proactive therapeutic drug monitoring and dosage adaptation, based on post-induction phase TLs, in predicting long-term GLM efficacy."

Berends et al. (2019) conducted a multicenter, prospective and observational trial (GO-KINETIC) in patients with moderate to severe ulcerative colitis (UC) receiving induction and maintenance treatment with golimumab (GLM) studying the associations between GLM exposure (serum concentrations and areas under the curve [AUC]) to include clinical and endoscopic outcomes. A total of twenty (n = 20) adult patients were enrolled. The primary outcome measured associations between drug exposure and clinical and endoscopic outcomes at week 8 and 52 after starting GLM therapy, using the simple clinical colitis activity index (SCCAI) and endoscopic Mayo score, respectively. Secondary outcomes measured the proportion of patients with detectable antibodies to GLM, evaluation of fecal GLM concentrations and biochemical response to GLM treatment (fecal calprotectin, serum C-reactive protein (CRP) and albumin). All patients started induction treatment with 200 mg GLM SC at day one and 100 mg SC at day 14. From week 6, maintenance treatment followed with 50 mg SC or 100 mg SC based on weight every four weeks. Serum samples were collected at day 0 and at day four, seven, 14, 18, 28, 42 and 56 to measure GLM serum concentrations, anti-GLM antibody levels, CRP and albumin concentrations. Fecal samples were collected for the measurement of fecal calprotectin and fecal GLM concentrations. During maintenance treatment, follow-up occurred at week 18, 21, 30, 33, 42, 45 and 52. Total follow-up was 52 weeks. Endoscopic response was defined as ≥ 1 point reduction in endoscopic Mayo score compared to baseline and endoscopic remission was defined as an endoscopic Mayo score ≤ 1. Endoscopic response and remission were assessed after induction and at week 8 and 52. Clinical activity was assessed during each study visit utilizing SCCAI. Clinical response and clinical remission were defined as a decrease in SCCAI of ≥ 3 points compared to baseline and SCCAI score ≤ 2. At week 8 endoscopic response was observed in 12 out 20 patients (60%) and 10/20 (50%) achieved endoscopic remission and two patients showed no endoscopic response. Due to clinical improvement 14 patients continued on GLM maintenance treatment, however, 7 out of the 14 patients (50%) lost their response after a median (IQR) treatment duration of 12 weeks. At week 52, three out of the initially included 20 patients (15%) were in clinical and endoscopic remission while continuing on GLM treatment. One of these patients had detectable anti-GLM antibodies at repeated measurements who continued on GLM maintenance treatment but was lost to follow-up. The authors stated, "the potential effect of immunogenicity on the pharmacokinetics of GLM could not be assessed in our study."

Section Summary: Etanercept (Enbrel) and Simponi/Simponi Aria (Golimumab)

For individuals with rheumatoid arthritis (RA), psoriatic arthritis (PsA) or juvenile idiopathic arthritis (JIA) or ulcerative colitis (UC) who receive evaluation of serum antibodies related to biologic agents Etanercept or Simponi/Simponi Aria, the evidence includes systematic review, cohort and observational studies. Relevant outcomes are test validity, change in disease status, health status measures, quality of life, and treatment-related morbidity. The systematic review by (Strand et. al. 2017) examined ten biologic agents which included Etanercept or Simponi/Simponi Aria and found that antibody (ADAb) rates varied widely among biologics across diseases and are not directly comparable because of immunoassay heterogeneity; the highest overall rates were reported with infliximab (0–83%), adalimumab (0–54%), and infliximab biosimilar CT-P13 (21–52%), and the lowest with secukinumab (0–1%), ustekinumab (1–11%), etanercept (0–13%), and golimumab (0–19%). ADAb+ versus ADAb- patients had lower rates of clinical

response to adalimumab (RA, PsA, JIA, AS, Ps), golimumab (RA), infliximab (RA, PsA, AS, Ps), rituximab (RA), ustekinumab (Ps), and CT-P13 (RA, AS). Higher rates of infusion-related reactions were reported in infliximab- and CTP13-treated ADAb+ patients. While there is evidence that has demonstrated an association between antidrug antibodies and secondary nonresponse as well as injection-site and infusion-site reactions. The clinical usefulness of measuring antidrug antibodies hinges on whether test results inform management changes, thereby leading to improved outcomes, compared with management directed by symptoms, clinical assessment, and standard laboratory evaluation. Limited evidence has described management changes after measuring ADAb. This systematic review found that further research is needed into immunogenicity and the potential benefits of ADAb monitoring, to include clinically validated, standardized ADAb assays to support this management approach.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Gastroenterology (ACG)

In 2019, the American College of Gastroenterology (ACG) published a guideline on ulcerative colitis (UC) which was updated in 2025. The guideline stated, “In patients with moderately to severely active UC who are responders to anti-TNF [tumor necrosis factor] therapy and now losing response, we suggest measuring serum drug levels and antidrug antibodies (if there is not sufficient drug present) to assess reason for loss of response (conditional recommendation, very low quality of evidence).”

In 2018, the American College of Gastroenterology (ACG) published a guideline on the management of Crohn’s disease (CD) which was updated in 2025. Although acknowledging that a detailed review of therapeutic drug monitoring was beyond the scope of the guideline, it stated: “If active CD is documented for persons receiving anti-TNF therapies, then assessment of anti-TNF drug levels and antidrug antibodies (therapeutic drug monitoring) should be considered.”

American Gastroenterological Association (AGA) Institute

In 2017, the American Gastroenterological Association (AGA) Institute published guideline on therapeutic drug monitoring in inflammatory bowel disease (IBD). 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:

"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 immunomodulator 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."

National Institute for Health and Care Excellence (NICE)

In 2016, the National Institute for Health and Care Excellence (NICE) issued guidance on therapeutic monitoring of TNF-α inhibitors in the treatment of patients with CD. The Institute recommended that laboratories monitoring TNF-α inhibitors in patients with CD who have lost response to the treatment should "work with clinicians to collect data through a prospective study, for local audit, or for submission to an existing registry."

In 2019, NICE issued guidance on therapeutic monitoring of TNF-α inhibitors in the treatment of patients with rheumatoid arthritis. The Institute stated: "Enzyme-linked immunosorbent assay (ELISA) tests for therapeutic monitoring of (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." It also recommended that "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."

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review can be located at clinicaltrials.gov.

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CODES

To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis codes.

Codes	Number	Description
CPT		
	84999	Unlisted chemistry procedure (when specified as Prometheus Anser IFX Testing, Prometheus Anser ADA, Prometheus Anser VDZ, or Prometheus Anser UST, DoseASSURE ADL, DoseASSURE GOL, DoseASSURE IFX, DoseASSURE UST or ADALX)
HCPCS		

Codes	Number	Description
	None	
Type of Service	Outpatient	
Place of Service	Laboratory	

POLICY HISTORY

Date	Action	Action
February 2026	Annual Review	Policy Renewed
January 2025	Annual Review	Policy Renewed
February 2024	Annual Review	Policy Revised
March 2023	Annual Review	Policy Revised
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	Annual Review	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

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