Regence

Medical Policy Manual Laboratory, Policy No. 65

Measurement of Serum Antibodies to Selected Biologic Agents

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Anti-drug antibodies to drugs such as infliximab, adalimumab, ustekinumab, and vedolizumab may be found in patients undergoing treatment for inflammatory diseases including inflammatory bowel disease, psoriasis, ankylosing spondylitis, or rheumatoid arthritis and are thought to be associated with a loss of treatment response.

MEDICAL POLICY CRITERIA

I. Measurement of serum antibodies to infliximab (Remicade, Inflectra, Renflexis) or adalimumab (Humira), either alone or as a combination test that includes serum drug levels, may be considered **medically necessary** for patients with inflammatory bowel disease (i.e., Crohn's disease or ulcerative colitis), when there is documentation of a loss of response to one of these medications.

II. Measurement of serum antibodies to infliximab (Remicade, Inflectra, Renflexis) or adalimumab (Humira), either alone or as a combination test that includes serum drug levels, is considered **not medically necessary** when there has not been a loss of response to the medication.

III. Measurement of serum antidrug antibodies, either alone or as a combination test that includes serum drug levels, is considered **investigational** for all of the following:

A. For any chronic inflammatory condition other than inflammatory bowel disease (i.e., Crohn's disease or ulcerative colitis), including but not limited to rheumatoid arthritis and psoriasis, and

B. For quantification of antibodies to ustekinumab, vedolizumab, certolizumab, etanercept, or golimumab for any condition.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Medication Policy Manual, Note: Click the link for the appropriate Medication Policy. Once the medication policy site is open, do a find (Ctrl+F) and enter drug name in the find bar to locate the appropriate policy.

BACKGROUND

INFLIXIMAB, ADALIMUMAB, USTEKINUMAB, AND VEDOLIZUMAB IN AUTOIMMUNE DISEASE

Therapy with monoclonal antibodies has revolutionized treatment of patients with inflammatory diseases such as inflammatory bowel disease (IBD; Crohn's disease [CD] and ulcerative colitis [UC]), rheumatoid arthritis and psoriasis. These agents are generally given to patients after conventional medical therapy fails, and they are typically highly effective for induction and maintenance of clinical remission. However, not all patients respond, and a high proportion of patients lose response over time. An estimated one-third of patients do not respond to induction therapy (primary nonresponse), and among initial responders, response wanes over time in approximately 20% to 60% of patients (secondary nonresponse). The reasons for therapeutic failures remain a matter of debate but include accelerated drug clearance (pharmacokinetics) and neutralizing agent activity (pharmacodynamics) due to anti-drug antibodies (ADA).[1]

Infliximab (Remicade® by Janssen Biotech, Inflectra® by Pfizer, and Renflexis® by Merck Sharp & Dohme) is an intravenous tumor necrosis factor alpha (TNFα) blocking agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis, CD, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and ulcerative colitis (UC). Infliximab is a chimeric (mouse/human) anti-TNFα monoclonal antibody. Adalimumab (Humira® AbbVie) is a subcutaneous TNFα inhibitor that is FDA-approved for treatment of the above indications (CD and UC in adults only) plus juvenile idiopathic arthritis (JIA). Adalimumab is a fully human monoclonal antibody to TNFα. Certolizumab (Cimzia® by UCB) is a subcutaneous TNFα inhibitor that is FDA-approved for treatment of rheumatoid arthritis, CD, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and non-radiographic axial spondyloarthritis (nr-axSpA). Etanercept (Enbrel®, Immunex) is a TNFα inhibitor that is FDA-approved for the treatment of rheumatoid arthritis, JIA, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. Golimumab (Simponi® by Janssen Biotech) is a subcutaneous TNFα inhibitor that is FDA-approved for the treatment of rheumatoid arthritis, ankylosing spondylitis, UC, and psoriatic arthritis. Vedolizumab (Entyvio®, Millennium Pharmaceuticals) is an intravenous blocking agent for integrin $\alpha_4\beta_7$ and is FDA-approved for adults with CD or UC. Ustekinumab (Stelara®, Janssen Biotech) is an antibody that blocks interleukins IL-12 and IL-23 and is FDA-approved to treat psoriasis and certain patients with Crohn's disease.

Following primary response to these medications, some patients become nonresponders (secondary nonresponse). The development of anti-drug antibodies (ADA) is thought to be a cause of secondary nonresponse. ADA are also associated with injection site reactions (adalimumab), and acute infusion reactions and delayed hypersensitivity reactions (infliximab). As a fully human antibody, adalimumab is considered less immunogenic than chimeric antibodies, such as infliximab.

DETECTION OF ANTI-DRUG ANTIBODIES

The detection and quantitative measurement of ADA has been fraught with difficulty owing to drug interference and identifying when antibodies are likely to 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 the radioimmunoassay (RIA) method, and more recently, the homogenous mobility shift assay (HMSA) using high-performance liquid chromatography. Disadvantages of the RIA method are associated with the complexity of the test and prolonged incubation time, and safety concerns related to the handling of radioactive material. The HMSA has the advantage of being able to measure ADA when infliximab is present in the serum. A reporter-gene assay (RGA) is also available, which allows for the measurement of ADAs capable of neutralizing drug activity.[2] Cell-based assays typically have difficulty in standardization, take up to two days to complete, and with effects from the serum matrix. However, the RGA can quantify the anti-drug neutralizing antibody independent of matrix effects within two hours. Application of the RGA has recently been assessed for use in a clinical laboratory setting, and found to be a precise and high-throughput robust platform for detection of ADA.[3] Large randomized studies are still necessary to establish relevant clinical cut-off levels. Studies evaluating the validation of results among different assays are lacking, making inter-study comparisons difficult. One retrospective study in 63 patients demonstrated comparable diagnostic accuracy between two different ELISA methods in patients with IBD (i.e., double antigen ELISA and antihuman lambda chain-based ELISA).[4] This study did not include an objective clinical and endoscopic scoring system for validation of results. A 2013 review by Seow and Panaccione, noted that the variability and lack of standardization in current assay tests has important implications for subsequent studies which report associations between antibodies-to-infliximab (ATIs) and infliximab levels and utilize these assays to predict treatment response.[5] These findings highlight the need for a validated gold standard test and established diagnostic parameters with which to measure levels of infliximab and ATIs.

TREATMENT OPTIONS FOR PATIENTS WITH SECONDARY LOSS OF RESPONSE TO ANTI-TNF THERAPY

A diminished or suboptimal response to infliximab or adalimumab can be managed in several ways: shortening the interval between doses, increasing the dose, switching to a different anti-TNF agent (in patients who continue to have loss of response after receiving the increased dose), or switching to a non-anti-TNF agent.

REGULATORY STATUS

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 the CLIA for high complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require regulatory review of these tests.

Prometheus® Laboratories Inc., a College of American Pathologists–accredited lab under CLIA, offers non-radiolabeled fluid-phase HMSA tests called the Anser® IFX test for infliximab. Anser® ADA for adalimumab, Anser® UST for ustekinumab, and Anser® VDZ for vedolizumab. None of these tests are ELISA-based and they can measure anti-drug antibodies in the presence of detectable drug levels, improving upon a major limitation of the ELISA method. All tests measure serum concentrations and anti-drug antibodies.

LabCorp has a portfolio of tests called DoseASSURE™ including DoseASSURE™ ADL for adalimumab, DoseASSURE™ UST for ustekinumab, DoseASSURE™ IFX for infliximab, DoseASSURE™ CTZ for certolizumab, DoseASSURE™ ETN for etanercept, and DoseASSURE™ GOL for golimumab. These tests are electrochemiluminescence immunoassay (ECLIA) and/or ELISA-based and report drug concentration and anti-drug antibody levels.

EVIDENCE SUMMARY

Validation of the clinical use of any diagnostic test focuses on analytic validity, diagnostic validity, and clinical utility. Analytic validity demonstrates technical feasibility as compared to a gold standard, including assessment of test reproducibility and precision. For comparison among studies, a common standardized protocol is necessary. Diagnostic utility is evaluated by the ability of a test to accurately predict the clinical outcome in appropriate populations of patients. For accurate interpretation of study results, sensitivities, specificities, and positive and negative predictive values compared to a gold standard must be known. Clinical utility is established when the evidence demonstrates that the diagnostic information obtained from a test can be used to benefit patient management and improve health outcomes. This evidence review focuses on the clinical validity and clinical utility.

Most studies evaluating antibodies to infliximab, adalimumab, ustekinumab, or vedolizumab report serum drug levels together with anti-drug antibody (ADA) levels, and correlate levels to disease response. Serum drug levels and disease response will not be addressed in this section and therefore the data reported on ADA will be highlighted from the identified studies. Most evidence concerning testing for ADA is derived from the data available for patients with inflammatory bowel disease (IBD) and rheumatoid arthritis (RA). Less literature exists concerning other diseases comprising psoriasis and spondyloarthropathies (SpA; i.e., ankylosing spondylitis, psoriatic arthritis, IBD-associated arthritis, reactive arthritis, and undifferentiated and juvenile SpA). There is also a lack of literature on the measurement of anti-vedolizumab and anti-ustekinumab antibodies for patient management.

CLINICAL VALIDITY

There is a substantial body of evidence examining associations of ADA with nonresponse and injection or infusion site reactions; numerous systematic reviews and meta-analyses have been published. Accordingly, the review of evidence concerning clinical validity focuses on the most current systematic reviews (see Tables 3 through 5) and studies published since those reviews,[6] as well as relevant studies not included in identified reviews (e.g., those focusing on adverse reactions and ADA).

Systematic Reviews

A systematic review (SR) published by Vermeire (2018) evaluated studies on immunogenicity to adalimumab (ADM), certolizumab pegol (CZP), golimumab, infliximab (IFX), ustekinumab, and vedolizumab in patients being treated for inflammatory bowel disease (IBD).[7] Although 122 publications covering 114 studies were noted as included in the review, all study designs and abstracts from conference proceedings were included. Greater than 90% of studies involved administration of ADM or IFX. Of the studies involving IFX administration, only 12 were RCTs and 62 were non-randomized or observational studies. Across these studies, rates of ADA formation were highly variable, ranging from 0.0–65.3% in patients with IBD. While the authors reported that the proportion of patients achieving and maintaining a response to treatment with IFX was “generally lower” for patients with detected ADA than those without detected ADA, no pooled analyses were reported for any study outcomes. No analysis informing clinically useful thresholds or timing of antibody testing was provided. This review was funded by Pfizer, Inc, a manufacturer of Inflectra, which is an infliximab biosimilar and multiple study authors are employees and/or stakeholders in Pfizer, Inc.

Six SRs published from 2012 through 2017 were identified.[8-12] The number of studies included ranged from 11[11] to 68,[12] varying according to review objectives and conditions of interest. Although not detailed here, there was considerable overlap in included studies across reviews.

A SR with meta-analysis by Pecoraro (2017) selected 34 studies (total n=4,273 patients), including randomized controlled trials (RCTs, n=4), prospective observational (n=22), retrospective observational (n=6), and cross-sectional studies (n=2).[13] Studies evaluated RA (n=18), ulcerative colitis (n=2), CD (n=5), psoriatic arthritis (n=4), ankylosing spondylitis (n=5), plaque psoriasis (n=4), spondyloarthritis (n=1). Most of the 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), and poor (n=1). The effect of ADA was evaluated in 19 studies, showing a significant ($p<0.05$) 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, $p<0.001$) than infliximab (RR 0.37, 95% CI 0.2 to 0.7, $p<0.001$). Measures of heterogeneity were 84%, 57%, and 79%, respectively. Fourteen studies reported on the effect of ADA on clinical response (see Table 1). Eleven studies found the risk of developing ADA to be significantly ($p=0.03$) lower in patients treated with concomitant methotrexate therapy relative to treated those 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 ($p<0.001$) 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 anti-tumor necrosis factor α (TNF-α) serum concentration (see Table 2). Of the 20 studies (n>2,800 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 (5%). Although ADA significantly reduced TNF-α response, the results should be viewed cautiously due to reported study limitations, including small numbers of studies included and considerable heterogeneity.

Freeman (2017) published a SR with meta-analysis evaluating the test accuracy estimates of levels of anti-tumour necrosis factor (anti-TNF) and antibodies to anti-TNF to predict loss of response or lack of regaining response in patients with anti-TNF managed Crohn’s disease (CD).[14] Studies of patients with CD treated with infliximab or adalimumab as well as studies

with mixed Crohn's and ulcerative colitis populations were included if the proportion of Crohn's patients was at least 70%. Twenty-four full-test reports and seven conference abstracts were included in the SR; eleven of the 31 studies examined infliximab trough levels, 20 examined levels of antibodies to infliximab and five and six studies, respectively, investigated adalimumab levels and antibodies to adalimumab. The greatest identified threat to validity of the studies was high risk of bias in patient selection, which was present in nearly 80% of the included studies. The studies were heterogeneous with respect to the type of test used (eg, commercial or in-house ELISA, radioimmunoassay (RIA), homogeneous mobility shift assay (HMSA)), criteria for establishing response or lack of regaining response (e.g., use of the Crohn's Disease Activity Index score or the physician's global assessment score) and population examined (responders or patients with secondary loss of response). Summary point estimates for sensitivity and specificity were 56% and 79% for antibodies to infliximab, respectively, and results for antibodies to adalimumab were similar. Positive and negative predictive values across all pooled studies ranged between 70% and 80%, implying that between 20% and 30% of both positive and negative test results may be incorrect in predicting loss of response. The authors concluded that "higher quality head-to-head test accuracy studies are required to enable differentiation between different types of tests and cut-offs, with consistent outcome measurement in the same population" and "more clinical trial evidence from test–treat studies is required before the clinical utility of the tests can be reliably evaluated."

A SR and meta-analysis by Thomas (2015) included 68 studies (14,651 patients) with patients with RA (n=8,766), SpA (n=1,534), and IBD (n=4,351) and examined the immunogenicity of infliximab (39 comparisons), adalimumab (15), etanercept (5), golimumab (14), and certolizumab (8).[12] The review identified studies published through December 2013 and included 38 RCTs and 30 observational studies (study quality rated as good [n=32], moderate [n=26], or poor [n=10]). The pooled prevalence of ADA varied with disease and drug (see Table 3, 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 ELISA assays. The presence of ADA was associated with lower odds of response across most drugs and diseases (see Table 4). An exception was in studies of IBD (similar to that reported by Lee [2012]). The 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 5) when ADA were detectable (OR 3.25, 95% CI 2.35 to 4.51). Evaluation of potential publication bias or overall assessment (e.g., GRADE or similar) for the body of evidence was not reported. Additionally, no measures of heterogeneity were reported.

A SR by Meroni (2015) included 57 studies of infliximab (n=34), adalimumab (n=18), and etanercept (n=5).[8] Studies included primarily patients with IBD and RA, but also SpA and psoriasis. Most studies were prospective cohort designs (n=42) and a formal assessment of study quality (bias) was not reported. The authors noted considerable variability in the time from drug administration to ADA and drug bioavailability testing across studies. Varied antibody testing assay methods were used and included solid-phases 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 3) but were consistent with other reviews. Qualitatively, the presence of ADA was associated with lower levels of infliximab and lower risk of disease control or remission. The presence of ADA also increased the risk of infusion reactions. When ascertained, the time to development of ADA varied from as little as 16 weeks to over a year. The time to ADA positivity varied – fifty percent of patients with detectable ADA at 28 weeks to a median time of one year. Finally, for

both infliximab and adalimumab, immunosuppression was associated with less ADA positivity. The authors concluded that "…the lack of homogeneity in study design and methodologies used in the studies analyzed limited the opportunity to establish the time-course and clinical consequences of anti-drug antibody development...." Although qualitative, the authors included many studies, and provided a detailed review of each study not reported by the other meta-analyses. The author's conclusions are consistent with the meta-analyses but with emphasis on important aspects of heterogeneity across studies.

Hsu (2014) published a SR of ADA in psoriasis that included 25 studies (n=7,969).[15] Inclusion criteria for the studies were: having at least 15 patients, documentation of serial assessments of psoriasis severity, and reporting ADA in patients with psoriasis receiving infliximab, etanercept, adalimumab, or ustekinumab. Ten of these studies reported on infliximab ADA: three found an association between ADA and lower serum infliximab levels, and five found an association between ADA and clinical response. Of the five studies that evaluated antiadalimumab antibodies, four found lower treatment efficacy for those with ADA. Six studies reported on ustekinumab ADA, and two of these found an association between ADA and Psoriasis Area and Severity Index (PASI) response. The remaining six studies in the review focused on antietanercet antibodies.

Nanda (2013) conducted a meta-analysis of studies that reported on clinical outcomes according to the presence or absence of ADA in patients with IBD.[11] MEDLINE, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Scopus databases were searched to February 2012, EMBASE to August 2012; 11 studies involving 707 patients were included. Six of these studies (two RCTs, one prospective cohort study, three retrospective cohort studies) were included in the meta-analysis by Lee (2012) outlined below. In at least one quality domain (study eligibility criteria, measurement of exposure and outcome, control for confounders, completeness of follow-up), all the included studies had high risk of bias. The prevalence of detectable ADA in the included studies ranged from 22.4% to 46% (see Table 3). The outcome of interest was 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 requirement for surgery or presence of nonhealing fistula. Patients with ATIs had a three-fold greater risk of loss of response than those without ATIs (RR 3.2, 95% CI 2.0 to 5.0) (shown in Table 3 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 (UC) 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 is limited by variability in the method of ADA detection (double-antigen ELISA, antihuman lambda chain-based ELISA, fluid-phase RIA). Study investigators stated, "[t]he true incidence of ADA in IBD patients treated with infliximab remains unknown due to the different administration schedules, timing of ADA measurements, methods used in ADA detection, and the presence of serum infliximab." Finally, although the authors noted that the funnel plot "suggested the presence of publication bias," the small number of studies and plot appearance (only two of 11 studies suggesting asymmetry) preclude conclusions.

Garces (2013) performed a meta-analysis of studies of infliximab and adalimumab used to treat RA, IBD, SpA, and psoriasis.[9] Databases were searched to August 2012, and 12

prospective cohort studies included involving 860 patients (540 with RA, 132 with SpA, 130 with IBD, 58 with psoriasis). The outcome of interest was response, assessed by using standard assessment scales for rheumatologic diseases (e.g., European League Against Rheumatism criteria for RA; Assessment in Ankylosing Spondylitis 20% response criteria, or ASDAS 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, 95% CI 0.22 to 0.48). 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 (2012) conducted a meta-analysis of patients with IBD receiving infliximab to estimate the prevalence of ADA, effect of ADA on the prevalence of infusion reactions, and the effect of ADA on disease remission rates.[10] Databases were searched through October 2011, and 18 studies involving 3,326 patients were included. Studies included nine RCTs, five prospective cohort studies, and four 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 3). Patients with ADA were less likely to be in clinical remission (Table 4), but this was not statistically significant (RR, 0.90, 95% CI 0.79 to 1.02, p=0.10). The rates of infusion reactions were significantly higher in patients with ADA (RR 2.07 [see Table 5], 95% CI 1.61 to 2.67). Immunosuppressants resulted in a 50% reduction in the risk of developing ADA (p<0.001). The meta-analysis concluded that patients with IBD 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.

Table 1. Effect of Anti-drug Antibodies on Clinical Response

Outcome Measures	No. Studies	MD	95% Confidence Interval	I^2, %	p
Disease Activity Score 28	9	0.93	0.41 to 1.44	84	<0.001
BASDAI	2	-0.62	-1.51 to 0.27	0	0.17
ASDAS	2	0.96	-0.27 to 2.2	0	0.13
Psoriasis Area Severity Index	1	4.7	-1.15 to 9.25	NR	0.04

Adapted from Pecoraro (2017).[13]
ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; I^2: heterogeneity measure; MD: mean difference; NR: not reported.

Table 2. Evaluation of Anti-TNF-α Concentration

Outcome Measures	No. Studies	MD, mg/L	95% Confidence Interval	I^2, %	p
ADA-positive vs ADA-negative	8	-7.07	-8.9 to -5.25	98	<0.001
Responders vs no responders	13	2.77	1.97 to 3.58	82	<0.001
Adalimumab therapy	6	5.07	3.77 to 6.36	62	<0.001
Infliximab	4	2.74	0.59 to 4.89	62	<0.001
Etanercept	3	0.85	0.41 to 1.13	82	<0.001
DAS28 change from baseline	8	-2.18	-2.91 to -1.44	97	<0.001

Adapted from Pecoraro (2017).[13]
ADA: anti-drug antibodies; DAS28: Disease Activity Score in 28 joints; I^2: heterogeneity measure; MD: mean difference; TNF: tumor necrosis factor.

Table 3. Estimated Prevalence of Anti-drug Antibodies from Meta-Analyses

Author	Included Studies	Drugs			Disease			Prevalence of ADA	
		IFX	ADL	Other[a]	IBD	RA	SpA	Pooled (95% CI)	Range in Studies
Lee (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 (2013)	11	●			●				22.4%-46%
Thomas (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 (2015)	14	●				●			19%-47%
	14	●			●				15%-61%
	5	●					●[d]		26%-50%
	12		●			●			5%-54%
	3		●		●				9%-46%
	3		●				●[d]		18%-45%

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

Table 4. Results from Meta-Analyses of Anti-drug Antibodies and Clinical Response

Author	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 (2012)	18	●			●			0.90 (0.79 to 1.02)		37%
Nanda (2013)	11	●			●			0.33 (0.20 to 0.40)		70%
Garces (2013)	12	●	●		●	●	●[b]	0.32 (0.22 to 0.48)		46%
Thomas (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

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] Includes etanercept, golimumab, certolizumab.
[b] Also psoriasis.

Table 5. Increased Risk of Adverse Reaction Associated With the Presence of Anti-drug Antibodies

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

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.

Nonrandomized Studies

Recent publications not included in the SRs above are included, below.

Bouden (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, spondyloarthritis, or Crohn's disease who were treated with either drug for at least 6 months.[16] The presence of ADA was detected in 40% of patients treated with infliximab and 25% with adalimumab, with the highest prevalence in spondyloarthritis (40%), followed by RA (35%) and Crohn's disease (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.

Bellur (2023) evaluated the frequency and clinical relevance of ADAs in 54 patients undergoing treatment with either adalimumab or infliximab for noninfectious uveitis.[17] None of the 12 patients receiving infliximab developed ADAs after a mean time between therapy initiation and testing of 1.7 years. One patient was a nonresponder. Of the 42 patients receiving adalimumab, ADAs were detected in 15 (35.7%). Mean drug levels were lower in patients with ADAs than in those without ($p<0.001$). ADAs were detected in a higher proportion of partial responders (50%) and nonresponders (53.8%) than complete responders (21.7%). The authors concluded that ADA detection may be associated with an increased risk of TNFα ineffectiveness, and ADA monitoring may be useful for determining TNFα therapy use, dosage, and frequency, but more research is needed.

A multicenter prospective cohort study of 137 patients with plaque-type psoriasis was published by De Keyser (2019).[18] Serum samples and Psoriasis Area and Severity Index scores were obtained at baseline, week 16, 28, 40, 52, and/or ≥64 of ustekinumab treatment. Presence of anti-ustekinumab antibodies (prevalence of 8.7%) was significantly associated with a diminished clinical response ($p=0.032$). The median ustekinumab trough concentration was 0.3 mcg/mL (<0.02-3.80). No differences in serum concentrations were observed between moderate to good responders and nonresponders ($p=0.948$). Although the authors found that the presence of anti-ustekinumab antibodies was associated with treatment response in this patient population, serial measurements were collected in less than half (43.8%) of the patients. Anti-ustekinumab antibodies was reported to have developed during the first 52 weeks of treatment, however, the number of observations in the first year of treatment (n=191) was significantly higher than the number of observations in patients on treatment more than one year (n=38). This may underestimate the prevalence of anti-ustekinumab antibody formation after long-term treatments. Ultimately, the authors concluded that while measurement of anti-ustekinumab antibodies should be considered if treatment response is unsatisfactory, additional research is needed to identify tools for TDM in psoriasis patients on ustekinumab treatment.

As part of a RCT of treatment strategies in rheumatoid arthritis (RA), Hambardzumyan (2019) analyzed serum infliximab (sIFX) and anti-drug antibodies (ADAs) levels in study participants randomized to methotrexate + infliximab therapy and for whom serial serum sampling data at three, nine, and 21 months were available (n=101).[19] The primary and secondary outcome measures were low disease activity [LDA = 28-joint Disease Activity Score (DAS28) ≤ 3.2] and remission (DAS28 < 2.6). The frequencies of very low sIFX levels increased over time, with 15%, 23%, and 28% at 3, 9, and 21 months from IFX start, respectively, and the majority of patients with very low sIFX levels were ADA positive at these time-points [71% (10/14), 82% (18/22), and 68% (19/28), respectively]. The proportion of patients with LDA was numerically higher at all follow-up time-points among those with sIFX ≥ 0.2 µg/mL compared with patients who had sIFX < 0.2 µg/mL and positive ADAs, although only significant at 21 months (67%

and 26%, p=0.002). Similar results were observed when remission was the outcome measure (47% vs 11%, p=0.004). The authors concluded that these findings support the monitoring of serum drug levels, however, these findings require validation in larger populations and for dose-adjustment studies.

Van den Berghe (2018) published a small study evaluating ADA to vedolizumab in a cohort of 40 patients with IBD.[20] This study included the development of an ELISA-based test to measure ADA in the presence of the drug. Antivedolizumab antibodies and vedolizumab trough levels were measured after six weeks of treatment and after treatment discontinuation. At the six-week follow-up, three (8%) of the patients were positive for ADA, but this appeared to be transient. None of the patients who discontinued vedolizumab were positive for ADA at the time of their last infusion or after discontinuation. The authors concluded that immunogenicity did not appear to play a major role in vedolizumab treatment failure.

Cludts (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.[21] 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 (SpA) due to axial involvement in all psoriatic arthritis patients. Although adalimumab levels varied among patients (0 to 30 µg/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 ADA 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 DAS28 and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores (p<0.001). There were no significant differences between BASDAI in ATA-positive compared with ATA-negative patients at 12 or 24 weeks. The study is 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 (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.[22] All patients experienced secondary nonresponse to adalimumab (n=65), etanercept (n=47), and infliximab (n=19) after six or more months of treatment. Serum ADA was identified in 48%, 0%, and 42% of patients of patients treated with adalimumab, etanercept, and infliximab, respectively. Loss of efficacy was assessed using the PASI (PASI >5), 75% improvement in PASI score from baseline (PASI75), and/or the Physician Global Assessment (PGA, >2). PGA values for ADA-positive vs ADA-negative patients were significantly worse in the adalimumab group (3.7 vs 3.2, p=0.02) but not in the infliximab group. There was a significant negative linear correlation between serum drug concentrations and ADA in both the adalimumab group (p=0.001) and among the three groups combined (p=0.001), and a significant (p=0.019) 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, 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 (2016) excludes possible confounding factors by analyzing adalimumab treatment for psoriasis in five 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.[23] The clinical severity of psoriasis was scored using the Psoriasis Area Severity Index (PASI). At 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 was no significant difference in median PASI score 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 its 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.

Chiu (2015) published a prospective observational study investigating the role of ustekinumab ADA in psoriasis.[24] The study included 76 individuals with plaque psoriasis who were treated with ustekinumab for at least seven months (mean 13 months). Antibodies to ustekinumab were found in five (6.5%) of the patients, and the presence of these antibodies was associated with lower serum levels of the drug ($p<0.001$) and lower PASI 50 response ($p=0.004$). Among the 15 patients who switched to ustekinumab from adalimumab, no difference in ustekinumab ADA was found between patients who had previously developed adalimumab ADA and those who did not.

Menting (2015) reported on the association between serum ustekinumab trough levels, ADA, and treatment efficacy in a small prospective study that included 41 patients with RA.[25] The mean follow-up time was 32 weeks (range 4 to 52 weeks), and during this period ADA to ustekinumab were detected in three patients. No correlations were seen between ustekinumab trough levels and clinical response to the medication.

While many studies have evaluated clinical validity using single ADA measurements, at least one study assessed their persistence over time. Vande Casteele (2013) analyzed infliximab trough and ADA levels using an HMSA assay with banked serum obtained from 90 IBD patients treated between May 1999 and August 2011.[26] ADA levels had been previously assayed using an ELISA-based test. A total of 1,232 samples were evaluated (mean 14 per patient). Treatment decisions were made solely on clinical evaluation and C-reactive protein levels. ADA were detected in 53 of 90 (59%) of patients but subsequently were nondetectable in 15 of the 53 (28%). Persistent ATIs were associated with discontinuation of infliximab (RR 5.1, 95% CI 1.4 to 19.0), but the wide confidence interval reflects considerable uncertainty. Although transience of ADA in IBD has not been carefully scrutinized, if replicated, these results suggest interpreting a single ADA result cautiously.

Section Summary: Clinical Validity

A large body of evidence has evaluated the clinical validity of ADA testing. ADA has been associated with secondary nonresponse in RA, SpA, IBD, and noninfectious uveitis. 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, a recent observational study found no association between concomitant immunosuppressants and anti-TNF immunogenicity in patients with psoriasis; and a second cohort study found no association between PASI score or TNF-α concentration and the presence of anti-adalimumab antibodies in patients receiving adalimumabto treat psoriasis.

CLINICAL UTILITY

Manceñido (2024) published a systematic review and meta-analysis to compare proactive therapeutic drug monitoring (TDM) to conventional management; i.e., reactive TDM, during maintenance treatment using anti-TNF-α factor for IBD.[27] The primary outcome measure was sustained clinical remission at 12 months. The analysis included nine studies, of which six were RCTs, and involved 528 patients. Proactive TDM was not found to be superior to conventional management in maintaining clinical remission at 12 months (RR 1.16; 95% CI 0.98-1.37, I^2=55%). The authors concluded that proactive TDM should not be recommended.

Several algorithms have been developed for management of patients with irritable bowel disease (IBD)[28-30] or rheumatoid arthritis (RA)[31] 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 has included evidence demonstrating improved health outcomes, such as reduced time to recovery from relapse (response), using algorithmic rather than dose-escalation approaches.

Syversen (2021) reported results of a randomized, parallel-group, open-label trial of 411 adults with RA, spondyloarthritis, 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 testing, or standard therapy without serum infliximab level or ADA testing (Norwegian drug monitoring [NOR-DRUM A]).[32] Serum trough infliximab levels and ADA levels 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 level was greater than 50 mcg/L at any point, therapy with infliximab was switched to a different agent. No significant difference between the therapeutic drug monitoring group and standard therapy group in clinical remission at week 30 was found (50.5% versus 53% of patients, respectively; p=0.78). 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%) of 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.Brun (2024) published a predefined exploratory analysis of data from the NOR-DRUM A and NOR-DRUM B studies. NOR-DRUM B, a 52-week trial, compared therapeutic drug monitoring to no monitoring (standard therapy) in 253 NOR-DRUM A participants and 205 newly enrolled participants on infliximab maintenance therapy.[33] The outcomes in accordance with therapeutic drug

monitoring were remission at week 30, disease worsening during 52 weeks, infusion reactions, and infliximab discontinuation. Therapeutic monitoring was not associated with ADA positivity and remission at day 30 (16/39 therapeutic monitoring and remission vs. 9/34 standard therapy and remission p=0.86). Therapeutic monitoring was associated with a lower risk of disease worsening (p=0.0001). The rate of disease worsening was highest in patients with ADA/standard therapy and lowest in patients without ADA but with therapeutic monitoring. The rate of infusion reactions (35 reactions in 28 patients) was higher in patients with antidrug antibodies, (p<0.0001). Therapeutic drug monitoring was associated with a lower risk of infusion reactions compared to standard therapy, and independent of ADA status (p=0.0076). Participants having therapeutic drug monitoring were more likely to discontinue infliximab and switch to another drug (p=0.037). The authors note that the treatment algorithm enabled switching therapy regardless of whether disease worsening had occurred, which is controversial. However, the authors point out that avoiding disease worsening is a worthwhile goal that may be achieved with therapeutic monitoring. The authors conclude that therapeutic monitoring may be of highest benefit to a subset of patients with ADA risk factors, such as predisposing HLA variants. Strengths of the study include its randomized design and high number of patients (n= 616). Limitations of the study includes its open-label design, its exploratory aim, and potential sparse data bias, especially regarding infusion reactions.

In a study of patients with IBD, Fernandex (2019) compared proactive monitoring of infliximab ADA and trough levels (n=56) to a retrospective control cohort (n=149).[34] The primary outcomes were hospital admission, surgery, treatment discontinuation, and rates of mucosal healing. A composite “unfavorable outcome” comprised of all of these was also analyzed. There was an association between treatment excalation rates and proactive monitoring (60.7% vs. 16.8% of controls, p<0.001). After two years of follow-up, surgery rates were lower in the proactive group (8.9% vs. 20.8%, p=0.030) and mucosal healing was more common (73.2% vs. 38.9%, p<0.0001). No significant differences were seen in hospitalization rate or treatment discontinuation.

A similar retrospective study by Papamichael (2019) evaluated proactive monitoring of serum adalimumab levels and ADA (n=53) with standard of care, defined as empirical dose excalation (n=279) or reactive monitoring (n=50).[35] Patients with early treatment failure (within eight weeks) were not included. After a median follow up of 3.1 years, fewer patients in the proactive monitoring group experienced treatment failure (hazard ratio [HR] 0.4, 95% CI 0.2 to 0.9). No significant difference was found for the probability of IBD-related surgery.

Kamperidis (2019) published retrospective observational study on the impact of therapeutic drug level monitoring (TDM) on outcomes of 291 patients with Crohn's disease treated with Infliximab (IFX).[36] Primary outcomes were clinicians' response to each TDM result and the rate of IFX discontinuation due to secondary loss of response or serious adverse event. Secondary outcomes included the intestinal surgery rate after IFX initiation and remission six months after TDM. Two hundred thirty-eight (81.8%) patients were tested for TDM at least once during their follow-up with 672 TDM results. 95/238 patients (39.9%) had undetectable levels and 76 (31.9%) had positive antibodies to infliximab (ATI) at least once. IFX was discontinued in 109 patients (37.5%). TDMs results were not followed by altered patient management in 526/672 (78.3%) of the observations. Treatment was discontinued in 40 (75.5%) patients never tested for TDM compared with 69 (29.0%) of those tested (p<0.01). Fewer TDM tested patients (29; 12.2%) required intestinal surgery post IFX initiation compared with those not TDM tested (15; 28.3%). In this retrospective study, data collected on clinical

outcomes relied on record keeping and physician response was taken as the measure of clinical remission. These methods may be subject to interpretation bias.

Dong (2019) reported an observational study of 60 patients with ankylosing spondylitis (AS) taking a biosimilar of etanercept.[37] Serum drug levels and anti-drug antibody levels, as well as clinical measures of disease activity were assessed at baseline and after four, 12, and 24 weeks of treatment. The authors found that anti-drug antibodies had no effect on the Assessment of Spondylosis Arthritis International Society (ASAS) remission rates but reported that patients with ADA had lower drug levels and higher TNF-α levels.

Steenholdt (2014) reported results of a noninferiority trial and cost-effectiveness analysis of 69 patients with CD who relapsed (CDAI ≥220 and/or ≥1 draining perianal fistula) during infliximab therapy.[38] Patients were randomized to infliximab dose intensification (5 mg/kg every four weeks) or algorithmic treatment based on serum infliximab level and ATI: Patients with subtherapeutic infliximab level (<0.5 µg/mL[39]) had infliximab dose increased if ADA were undetectable or were switched to adalimumab if ADA were detectable; patients with therapeutic infliximab level underwent repeat testing of infliximab and ADA levels if ADA were detectable or diagnostic reassessment if ADA were undetectable. Serum infliximab and ADA levels were measured in all patients using RIA 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 arm[40] 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 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 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 (2014) conducted a single-center, prospective observational study of 82 patients with IBD (n=45 CD, n=27 UC) with clinical relapse (CDAI >220 or Mayo Clinic >5) during treatment with adalimumab 40 mg every two weeks.[41] For all patients, trough adalimumab levels and ADA 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 four 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 six months were compared across three groups: (1) those with a therapeutic adalimumab level (>4.9 µg/mL[42]), (2) those with a subtherapeutic

adalimumab level and undetectable ATA; and (3) those with a subtherapeutic adalimumab level and detectable ADA. 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 five months) and group 3 (mean, four months, p<0.01 for both comparisons vs group 2). At one 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 did not 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, three months) and group 2 (mean, five months, p<0.01 for both comparison vs group 3). At one 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 IBD who relapse on adalimumab and have subtherapeutic serum adalimumab levels may benefit from a higher adalimumab dose if ADA are undetectable or from a change to another TNF inhibitor if ADA 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 ADA monitoring. However, results were influenced by the small sample size, use of ELISA for antibody testing, and lack of ADA levels for decision making. Studies comparing management using the algorithm proposed with usual care are needed.

Afif (2010) evaluated the clinical utility of measuring ADA (referred to as human antichimeric antibodies [HACA] in the study) and infliximab concentrations by retrospectively reviewing patient medical records.[43] Record review from 2003 to 2008 identified 155 patients who had had ADA, 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 loss of response to infliximab (49%), partial response after initiation of infliximab (22%), and possible autoimmune or delayed hypersensitivity reaction (10%). ADA 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 measurement of ADA and infliximab concentration had a clinically useful effect on patient management. The strategy of increasing infliximab dose in patients with ADA 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 using ELISA testing for ADA. Because there was no control group, one cannot determine what changes in management would have been made absent ADA 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 ADA are measured.

Section Summary: Clinical Utility

Significant evidence for the clinical utility of ADA testing is currently lacking. 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.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF GASTROENTEROLOGY

In 2019, the American College of Gastroenterology published a guideline on ulcerative colitis (UC).[44] The guideline stated: "In patients with moderately to severely active UC who are responders to anti-TNF therapy and now losing response, we suggest measuring serum drug levels and antibodies (if there is not a therapeutic level) to assess the reason for loss of response (conditional recommendation, very low quality of evidence)."

In 2018, the American College of Gastroenterology published a guideline on Crohn’s disease (CD).[45] Although acknowledging that a detailed review of therapeutic drug monitoring was beyond the scope of the guideline, it stated: "If active CD is documented, then assessment of biologic drug levels and antidrug antibodies (therapeutic drug monitoring) should be considered."

AMERICAN GASTROENTEROLOGICAL ASSOCIATION

In 2024, the American Gastroenterological Association published a clinical practice guideline on pharmacological management of moderate to severe ulcerative colitis. The guideline does not address the use of serum antibody measurement or therapeutic drug monitoring. [46]

In 2017, the American Gastroenterological Association published an evidence-based clinical practice guideline on therapeutic drug monitoring (TDM) in inflammatory bowel disease (IBD).[47] The guideline was developed according to the GRADE framework to evaluate certainty of evidence, and a Technical Review was published to accompany the recommendations.[48] Regarding measurement of anti-drug antibodies, the Association made the following statement:

> “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.*

According to the GRADE method, *very low quality* is defined as: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

The guideline also stated:

> "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.*

AMERICAN COLLEGE OF RHEUMATOLOGY

The American College of Rheumatology published a clinical practice guideline on axial spondyloarthritis in 2019.[49] The guideline includes recommendations for treatment with TNFα inhibitors for people with active and stable ankylosing spondylitis. The guideline does not address the use of serum antibody measurement.

The American College of Rheumatology published a clinical practice guideline on the pharmacologic management of rheumatoid arthritis in 2021.[50] The guideline includes recommendations for treatment with TNFα inhibitors. The guideline does not address the use of serum antibody measurement.

SUMMARY

Antibodies to drugs for chronic inflammatory diseases including, but not limited to infliximab, adalimumab, ustekinumab, certolizumab, etanercept, golimumab, and vedolizumab, are present in a substantial number of patients treated with these medications. A correlation between the level of these antibodies and clinical response has been identified in patients with some chronic inflammatory conditions.

There is some evidence that, in patients with inflammatory bowel disease who have lost response to infliximab or adalimumab, measurement of serum drug antibodies can impact patient care decisions. Evidence-based clinical practice guidelines recommend reactive monitoring of serum drug levels and anti-drug antibodies to guide treatment changes in patients with active inflammatory bowel disease who are being treated with an anti-TNF agent. Therefore, measurement of serum antibodies to infliximab (Remicade, Inflectra, Renflexis) or adalimumab (Humira), either alone or as a combination test that includes serum drug levels, may be considered medically necessary for patients with inflammatory bowel disease (i.e., Crohn's disease or ulcerative colitis) when there is documentation of a loss of response to these medications.

There is not enough evidence to show that measurement of serum drug antibodies, either alone or as a combination test that includes serum drug levels, improves net health outcomes when there has not been a loss of response to the medication. No evidence-based clinical practice guidelines recommend the measurement of serum drug antibodies when there has not been a loss of response to medication. Therefore, measurement of serum drug antibodies, either alone or as a combination test that includes serum drug levels, is considered not medically necessary when there has not been a loss of response to the medication.

There is not enough research to determine whether measurement of serum anti-drug antibodies can be used in patient management to improve net health outcomes for all conditions. The optimal timing of when to measure antibody levels and measurement cutoff levels has not been established. No evidence-based clinical practice guidelines recommend testing for serum drug antibodies in the treatment of chronic inflammatory conditions other than anti-TNF agents in the treatment of inflammatory bowel disease. Therefore, measurement of serum drug antibodies, either alone or as a combination test that includes serum drug levels, other than infliximab or adalimumab in the treatment of inflammatory bowel disease, is considered investigational.

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CODES

Codes	Number	Description
CPT	80145	Adalimumab
	80230	Infliximab
	80280	Vedolizumab
	80299	Quantitation of therapeutic drug, not elsewhere specified
	84999	Unlisted chemistry procedure
HCPCS	None	

Date of Origin: *January 2013*