REVIEW

Assessing Response and Loss of Response to Biological Therapies in IBD

Henit Yanai, MD[1] and Stephen B. Hanauer, MD[2]

OBJECTIVES: **The advent of biological therapies for inflammatory bowel disease (IBD) began in 1998 with the approval of infliximab for the treatment of refractory (to conventional agents) Crohn's disease (CD). Since then, the indications for anti-tumor necrosis factor-α (anti-TNFα) therapy have increased to include induction and maintenance of clinical responses and remissions for luminal and fistulizing CD, the treatment of children with CD, and the treatment of adults with ulcerative colitis. Additional utilities of biological therapies have included demonstrable mucosal healing, improvement in quality of life, reduction in surgeries and hospitalizations, and the treatment of extraintestinal manifestations of IBD including central and peripheral arthritis and pyoderma gangrenosum. Natalizumab has also been approved for the treatment of refractory Crohn's in patients who have failed conventional agents and anti-TNFα therapies. Unfortunately, despite the overall effectiveness of biological agents in a spectrum of indications for IBD, a significant proportion of patients do not respond or lose response over time. In this review, we intend to appraise the latest evolution in treatment strategies in IBD and to suggest an evidence-based approach and risk stratification while coping with cases of non-responders or loss of response to biological therapies.**

METHODS: **We conducted a literature search of English publications listed in the electronic databases of MEDLINE (source PUBMED) and constructed an analytical review based on definitions of response and loss of response, considering potential responsible mechanisms, clinical assessment tools, and finally recommending a practical approach for its prevention and management.**

RESULTS: **Favorable clinical outcome appears to be the consequence of sustained therapeutic drug levels, and the current literature supports a practice of dose adjustments. When immunogenicity develops to a single biological agent, response can be regained by introduction of an alternative biological agent of the same or different class. Efficacy is reduced with second-line agents either within or across classes compared with naive patients. In the absence of direct measurement of drug levels and anti-drug antibodies, clinical judgment is necessary to assess the mechanisms of loss of response, and more empiric decision making may be necessary to determine the choice of second-line biological agents. Optimal treatment strategies are still controversial.**

CONCLUSIONS: **It is essential to recognize the spectrum of mechanisms affecting response and loss of response to form a logical and efficient management algorithm, and, perhaps, it is time to incorporate the measurement of trough levels and anti-drug antibodies in the strategy of such an assessment. Prospective controlled trials are direly needed to investigate the optimal tailored management in individual patients who lose response.**

Am J Gastroenterol 2011; 106:685–698; doi:10.1038/ajg.2011.103; published online 22 March 2011

CASE 1: PRIMARY NON-RESPONSE

A 28-year-old male with a 10-year history of ileocolonic Crohn's disease (CD) was admitted to the hospital with a recent onset of fever, profound diarrhea, and localized right lower quadrant abdominal pain associated with a 10-pound weight loss over the past 6 weeks. He had been doing fairly well for several years while

[1]IBD Center, Section of Gastroenterology and Liver Diseases, Tel-Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; [2]Section of Gastroenterology and Nutrition, University of Chicago Medical Center, Chicago, Illinois, USA. **Correspondence:** Stephen B. Hanauer, MD, Section of Gastroenterology and Nutrition, University of Chicago Medical Center, 5841 South, Maryland Avenue, MC 4076, Chicago, Illinois 60637, USA. E-mail: shanauer@medicine.bsd.uchicago.edu
Received 10 November 2010; accepted 1 March 2011

being treated with 100 mg of 6-mercaptopurine daily (1.5 mg/kg body weight). Three weeks before his admission, following colonoscopic corroboration of active CD, he was started on prednisone (40 mg daily), but reported no benefit.

On physical examination, the patient was found to be tachycardic, with a pulse rate of 110 beats per min, a blood pressure of 100/70 mm Hg, and a temperature 101.3 F° (38.5 C°), but was in no apparent distress. His bowel sounds were normoactive and his abdomen was soft but mildly distended, with evidence of a localized tender mass in the right lower quadrant. The remainder of the physical examination was unremarkable.

Laboratory test results demonstrated an elevated C reactive protein (CRP) of 25 mg/l, decreased albumin of 3.3 mg/dl, and mild anemia with hemoglobin of 10.3 g/dl. Stool culture and examination for ova and parasites were negative. *Clostridium difficile* toxin A/B assay in stool was negative.

Colonoscopy revealed patchy colitis, which manifested as edematous, granular, and friable mucosa in the ascending colon and cecum, shallow linear ulcerations on the ileocecal valve, and multiple diffuse and deep ulcerations affecting at least the distal 12–15 cm of the terminal ileum. Histology demonstrated moderately active and chronic inflammation in the ascending colon, cecum, and ileocecal valve, and severely active and chronic inflammation with ulcerations and granulomas in the terminal ileum. The findings were compatible with severe active CD.

Computed tomography enterography demonstrated narrowing of the terminal and distal ileum lumen with wall thickening measuring ~20 cm in length. There was also thickening of the cecum and ascending colon wall. There was no evidence of free air or abscesses. Bowel loops proximal to the narrowed segment were mildly dilated with air fluid levels. Moderately enlarged mesenteric lymph nodes were seen adjacent to the distal ileum.

Steroid-refractory CD flare was confirmed and infliximab was introduced. Induction was obtained with two infusions of infliximab 5 mg/kg body weight at weeks 0 and 2; however, the patient failed to respond. Having failed infliximab induction, treatment options included trial of another biological agent vs. surgical resection. The patient opted to proceed with surgery.

CASE 2: LOSS OF RESPONSE

A 29-year-old female with a 10-year history of ileocolonic CD was referred for consultation because of persistent diarrhea and abdominal pain.

Following initial diagnosis, she had been treated with sulfasalazine and had done well for several years. However, the patient relapsed 4 years later with severe diarrhea, abdominal cramps, and weight loss. She responded to a course of steroids and was then started on azathioprine (AZA), on which she did reasonably well for several years, although with occasional waxing and waning of symptoms while being maintained on AZA (150 mg daily; 2 mg/kg body weight) and sulfasalazine (4 g/day).

Two years before her most recent presentation, the patient had gone through another significant relapse. Infliximab was initiated with a three-dose induction regimen of 5 mg/kg body weight at weeks 0, 2, and 6, with significant improvement shortly after the first infusion. The patient continued maintenance scheduled therapy with a regimen of infliximab infusion (5 mg/kg body weight) at every 8 weeks in combination with AZA, and for about a year she did well.

Approximately 1 year after initiating infliximab, she began to notice breakthrough symptoms between infusions that initially improved with each subsequent infusion of infliximab. However, over time the duration of the period of relief decreased and she complained of frequent loose stools accompanied by urgency and abdominal cramps. Colonoscopy demonstrated severe ileitis and moderate patchy colitis affecting the cecum, ascending, and descending colon. The interval between infliximab infusions was shortened to every 6 weeks, but over the ensuing months, she continued to report diminishing benefit from each infusion, with progressively shorter duration of symptom relief. Increasing the dose of infliximab to 10 mg/kg had minimal effects. Four weeks after her last infliximab infusion, serum infliximab levels were measured and reported as below the detection threshold of the commercially available assay, and antibodies to infliximab (ATI; formerly HACA, human anti-chimeric antibodies) were detected. At that point, the patient was considered to have "lost response" and infliximab therapy was discontinued and switched with adalimumab. She was given an induction regimen of adalimumab (160 mg) subcutaneously, followed by 80 mg 2 weeks later, and then maintenance therapy with 40 mg every other week. Following initiation of adalimumab, she reported significant and persisting benefits.

INTRODUCTION

Idiopathic inflammatory bowel disease (IBD), including CD, ulcerative colitis (UC), and indeterminate colitis, are chronic inflammatory disorders defined by distinctive clinical, pathological, endoscopic, and radiological features. IBD can occur at any age, but most typically presents in the second or third decade; the majority of affected individuals develop chronic, relapsing symptoms in the absence of medical therapy. The clinical presentation of IBD varies according to the location, extent, and severity of mucosal inflammation. The diversity of clinical symptoms and the varied therapies pose a substantial psychological burden and can greatly decrease the quality of life for patients. The pathogenesis of IBD is not well understood. Complex interactions between genetic and environmental risk factors contribute to susceptibility.

Two basic mechanisms comprise the immunopathogenesis of IBD: dysregulation of the normal immune response directed against luminal bacteria or their products, and inappropriate immune responses to organisms in the intestine that normally do not elicit a response, possibly because of intrinsic alterations in mucosal barrier function. Chronic, active inflammation is the end result of the dynamic balance between commensal flora and host defensive responses at the mucosal frontier. The innate immune response appears to be a prerequisite for excessive activation of the adaptive immune system and tissue damage. A detailed discussion

of the complex interrelations is beyond the scope of this article, and excellent reviews have been published elsewhere (1–4).

Until the late 1990s, when the first biological therapy was approved for use in CD, the conventional arsenal of therapies in IBD comprised corticosteroids, antibiotics, aminosalicylates, and immunomodulators. Corticosteroids have been used in the treatment of active IBD for induction of clinical remission; however, they are not effective for maintenance of remission, often lead to steroid-dependence, and their long-term use can be associated with severe and potentially irreversible side effects. AZA, 6-mercaptopurine, and methotrexate are effective steroid-sparing drugs that facilitate maintenance of remission but suffer considerable failure rates, and their effect on the natural history of the disease and on the need for surgery remains largely unknown.

Biologics and new goals of therapy

Over the past several decades, new therapeutic options have arisen for the treatment of the IBD and other immune-mediated diseases. These therapies, referred to as biologics (naive proteins, cytokines, growth factors, and antibodies) are produced by biotechnology. Biologics interfere in different ways with molecules that are involved in the disease pathogenesis. Initially, biologics targeting tumor necrosis factor-α (TNFα) were approved for patients with persisting signs and symptoms of disease refractory to conventional agents, and they have proved to have a dramatic impact in achieving new therapeutic goals. Novel biological therapies targeting different specific immunological pathways continue to be developed and introduced for a variety of clinical scenarios in IBD. The present treatment goals include rapid induction of clinical remission, steroid-free maintenance of clinical remission, mucosal healing in luminal disease, healing of CD fistula, avoidance of hospitalizations and surgeries, and improvement of quality of life. The ultimate goal of therapy will be the ability to prevent long-term complications of progressive disease such as the development of strictures, fistulae, neoplasia, extraintestinal symptoms, or the need for surgery.

Anti-TNFα agents

TNFα is a trimeric molecule with two bioactive forms, membrane-bound TNFα and soluble TNFα. The membrane-bound form of TNFα signals into the cell through its cytoplasmic domain. TNFα is a proinflammatory cytokine with a wide range of effects including upregulation of adhesion molecules responsible for local recruitment of circulating lymphocytes, induction of matrix metalloproteinases found in the lamina propria, activation of additional proinflammatory pathways, and formation of granulomas. In addition to binding to circulating (soluble) TNFα, monoclonal antibodies targeting TNFα bind to membrane TNFα and induce "reverse signaling" into cells, inhibiting TNFα-induced activation of NF-κB and activation of downstream mediators of inflammation (5). It appears that this proinflammatory cytokine, at least in part, mediates the inflammation in IBD (6–8), and blocking TNFα has had demonstrable benefits in a spectrum of IBD scenarios and other chronic immune-mediated inflammatory disorders such as rheumatoid arthritis, ankylosing spondylitis, and psoriasis.

Infliximab, a chimeric murine–human IgG1 monoclonal antibody targeting TNFα was the first biological agent to be approved for the therapy of CD, and has an established efficacy and safety profile (9–11). Infliximab is administered as an intravenous infusion (induction at weeks 0, 2, and 6, followed by maintenance with regular interval of every 8 weeks). The exact mechanism of action for infliximab has not yet been fully elucidated (5). Infliximab not only neutralizes circulating and membrane-bound TNFα but also lyses activated T cells and macrophages and induces T-cell apoptosis (12). Clinical studies have demonstrated that infliximab can induce and maintain remission of luminal disease, induce and maintain fistula closure, spare the need for steroids, induce and maintain mucosal healing, reduce hospitalizations and surgeries, and improve quality of life (9–11,13). Currently, infliximab is approved for treatment of both CD and UC that have not adequately responded to conventional therapies.

Two other anti-TNFα molecules have been approved for therapy of CD, namely, adalimumab, a fully humanized IgG1 anti-TNFα monoclonal antibody, and certolizumab pegol, a humanized monoclonal Fab′ fragment with a high binding affinity for TNFα attached to two polyethylene glycol molecules to prolong the pharmacological availability in circulation and tissues (certolizumab pegol is approved and used mainly in the United States and in only a few other countries). Both agents are administered as subcutaneous injections (each have a specific induction dosing regimen followed by regular maintenance injection intervals accordingly). Both agents bind and inactivate soluble and membrane-bound TNFα, and have demonstrated efficacy and safety for the treatment of CD in well-designed, randomized, controlled trials (14–22).

In contrast, etanercept is a soluble TNF receptor fusion protein (humanized IgG1 Fc fragment fused with two identical humanized p75 TNF receptors) that binds and inactivates soluble, but not membrane-bound TNFα, and although effective for the treatment of rheumatoid arthritis and other forms of inflammatory joint diseases, etanercept failed to demonstrate efficacy at similar doses in a clinical trial for CD (23). Of note, the effective dosing strategies of infliximab, adalimumab, and certolizumab pegol in IBD have been substantially higher than in rheumatological disorders, posing the issue of whether sufficient doses of etanercept were used.

Whether fully "human", "humanized", or chimeric, biological therapies are comprised of non-naturally occurring (or produced) protein structures that are associated with a risk of immunogenicity, the development of an immune response against foreign protein (24). Immunogenicity may be associated with acute or delayed infusion reactions and decreased effectiveness of therapy (25–27). Aside from the risk of infusion reactions that are primarily observed with infliximab, all anti-TNFα agents have similar safety profiles. Anti-TNFα-directed therapy is associated with increased risks of infections, particularly with intracellular pathogens such as *Mycobacterium tuberculosis*. However, the main risk of infection is conferred to combination immunosuppression and mainly

to concomitant steroid use (28–30). Infusion (infliximab) and injection site reactions occur with all anti-TNFα agents, although rates vary by mode of administration. Patients frequently develop serological evidence of autoimmunity (elevated concentrations of antinuclear antibodies) after exposure to anti-TNFα agents; although the frequency of autoantibodies is less with adalimumab and certolizumab pegol, the relevance of these autoantibodies is usually innocuous, as drug-induced lupus is rare. Another concern regarding anti-TNFα therapies has been the development of neoplasias, primarily lymphomas, as reported in a recent meta-analysis of all clinical trials with anti-TNFα agents (31). Several cases of aggressive hepatosplenic T-cell lymphomas, mostly in young males, associated with combination of anti-TNFα and thiopurines and triggered concern from concomitant therapy, specifically in the pediatric population (32,33). Neurological events (demyelination) and congestive heart failure are rare side effects that preclude any anti-TNFα formulations because of an assumed "class effect."

In the absence of direct comparison between anti-TNFα biological agents in head-to-head trials, it is difficult to compare their efficacy. Clinical trials for the three anti-TNFα agents approved for CD or UC have used different end point criteria and response time, in addition to the different modes of administration. Interpretations of these differences and their overall clinical relevance remain controversial. Nevertheless, when optimally dosed, all three approved agents have been effective in their ability to induce response and maintain remission.

Despite the revolutionary impact that biological therapy has had for the treatment of IBD, the efficacy of anti-TNFα is limited. A total of 20–30% of patients with refractory CD (9,14,16,18,19,21,22) and roughly 40% of patients with refractory UC (34) do not respond to anti-TNFα treatment and are defined as primary failures. In addition, long-term therapy with biologics is associated with significant loss of response (up to 40%) (9) and episodic (in contrast to maintenance) dosing, and "drug holidays" may lead to development of immunogenicity, infusion/injection reactions, and intolerance. These issues have elicited considerable debate regarding the most appropriate strategies to minimize the impact of such events.

Biologics other than anti-TNFα

Recently, natalizumab, a humanized IgG4 monoclonal antibody that antagonizes integrin heterodimers containing α4-integrin, was approved as a second-line biologic for therapy in the United States for CD patients who failed conventional therapies. Natalizumab inhibits leukocyte trafficking by preventing α4-mediated adhesion of leukocytes to adhesion molecules and transmigration of leukocytes across endothelium into inflamed mucosa (35,36). Natalizumab is well tolerated, but is associated with an increased risk for infections, acute hypersensitivity reactions, and hepatotoxicity. The primary concern regarding natalizumab therapy has been the reactivation of latent human JC polyomavirus that can lead to a fatal central nervous system infection, progressive multifocal leukoencephalopathy, which has an estimated risk of 1:1,000 (37). Therefore, natalizumab use has been restricted to monotherapy, without concomitant immune suppressants, and has a mandated special safety monitoring program and consent that has limited its patient acceptance. Nevertheless, natalizumab remains a viable option for patients who have lost a mechanistic response to anti-TNFα agents (see below).

ASSESSING RESPONSE TO THERAPY IN IBD

The primary goals of therapy for IBD are induction and maintenance of clinically defined remission. Most recently, the ability of infliximab to induce "mucosal healing" in both CD and UC has provided a semi-quantifiable measure of direct anti-inflammatory effect separate from symptom- and sign-based indices (38) that have not correlated with modification of the disease course. In contrast to rheumatoid arthritis, assessments of long-term outcomes in IBD, particularly in CD, is impeded by the absence of a readily determined measure of "structural damage" that have been incorporated into clinical trial end points. Although accurate and objective assessments of disease activity are important for prognostic reasons and for therapeutic decision making, in clinical practice, it is usually sufficient to follow patient's signs and symptoms. Hence, clinical remission would be defined as restoration of normal bowel function, quality of life, and elimination of steroids. Clinical response would be defined as improvement in these parameters. Yet, when correlated with surrogate outcomes for "disease modification" such as the need for hospitalizations and surgeries, mucosal healing is a more reliable end point than reduction in disease activity by index scores such as the Crohn's disease activity index (CDAI) or clinical activity index in UC (38). Furthermore, direct evidence of mucosal ulceration in both CD and UC is a factor that separates placebo responders from "active comparators" in randomized controlled trials (RCTs) (39).

ASSESSING RESPONSE AND NON-RESPONSE TO ANTI-TNFα

Primary non-response

The clinical definition of primary non-response is lack of improvement of clinical signs and symptoms with induction therapy. However, definitions and time-frames for the assessment of response and non-response have varied amongst clinical trials for different biological agents. In the original "Targan" study of infliximab in refractory CD, response was defined as a 70-point reduction in the CDAI after 4 weeks (11). Subsequently, in the ACCENT I study of infliximab, which assessed the maintenance benefits of infliximab, the initial response was defined as a 70-point reduction in the CDAI at 2 weeks (9); most clinicians will consider lack of response after two consecutive infusions of infliximab of at least 5 mg/kg body weight and will asses treatment failure at 4 weeks (12). However, recent data suggest that patients who initially respond may, more gradually, accrue remissions over time (19). As all three currently approved anti-TNFα biological agents are administered differently and have different pharmacokinetics and dosing intervals, a reasonable assessment of lack of response to adalimumab and certolizumab pegol would be made after completion of induction therapy at 4 and 6 weeks,

respectively (12), with recognition that attainment of criteria for remission may require a longer period of time on therapy (up to 12 weeks or longer in the experience with adalimumab).

In clinical trials for all biologics, approximately one-third of patients do not respond to an inductive regimen (9,14,16,19,21). Lack of response may be due to different immunoinflammatory mechanism(s), a differential role of TNFα in certain stages of disease, individual differences in drug metabolism and elimination, drug binding in serum or tissues based on disease activity level (40,41), the presence of innate anti-TNFα antibodies that may exhibit greater neutralizing activity in non-responders (42), absence of inflammation accounting for clinical symptoms, or impacted by, as yet unidentified, genetic or serological backgrounds of individual patients (5).

To date, the most predictive factor of response to anti-TNFα therapy in CD is a short-duration of disease and inflammatory, but not stricturing, disease (43–46). Patients with longer disease duration may have "non-inflammatory" symptoms related to strictures, bacterial overgrowth, and/or a motility disorder that does not respond to anti-inflammatory therapy. Other clinical predictors of response are colonic disease, less severe disease, and non-smoking. Among inflammatory markers, only CRP has consistently correlated with placebo responses in clinical trials, that is, CRP concentrations were inversely correlated with rates of placebo response (12). Finally, pharmacogenomic studies have suggested genetic markers as potential predictors of response to anti-TNFα therapies; however, findings have been inconsistent and require further validation and reproduction before implementation in clinical practice (47–50).

Secondary non-response

In contrast to primary non-response, a proportion of patients treated with anti-TNFα therapy, who meet the criteria for an initial clinical response, eventually lose response. Loss of response, also referred to as secondary non-response, is defined as recurrence of disease activity during maintenance therapy after achieving an appropriate induction response. However, assessing and defining loss of response can be even more complex than defining an initial response. Loss of response can be related to individual differences in bioavailability and pharmacokinetics, leading to inadequate concentrations of a biologic secondary to immunogenicity or other factors that increase drug clearance (decreased circulation half life and possible high consumption in severe disease) (25,40). Loss of response can also be related to a shift in the dominant mechanism of inflammation (loss of the pharmacodynamic effect), increasing symptoms or signs not related to IBD activity (for example, irritable bowel syndrome, concomitant infection, bacterial overgrowth, and so on), or failure to wean off corticosteroids. Loss of response can also imply a "relative" term for patients who have shorter durations of response (for example, less than 4 weeks for infliximab, 1 week for adalimumab, or 2 weeks for certolizumab) or require dose escalation, which may become economically impractical.

When assessing loss of response, the first step should always be an evaluation to identify and confirm the presence of active IBD rather than a fixed stenosis, superimposed infection, or irritable bowel symptoms, which may present with similar symptoms.

Immunogenicity is a frequent contributor to secondary loss of response. As already mentioned, immunogenicity may develop against any biologic (24). Immunogenicity is associated with anti-drug antibodies, although the impact of anti-drug antibodies is variable on both pharmacokinetic and pharmacodynamic activity. Even fully humanized monoclonal antibodies may elicit the development of anti-drug antibodies, however, probably to a lesser extent (24,27,51). Most of the data in the literature refer to ATI because of its longer duration of marketing and world-wide study and, in the United States, the commercial availability of assays. Anti-drug antibodies may decrease the drug bioavailability and alter pharmacokinetics. Anti-drug antibodies can prevent the drug from entering the circulation and reaching the inflammation site, enhance clearance, or prevent proper absorption through immune complex formation and prevent the drug-neutralizing potency (52). Anti-drug antibodies have been associated with increased risk of infusion or injection reactions (depending on the agent and the mode of administration), which in turn may lead to decreased serum drug levels and shorter duration of response (24–26,53–55). Anti-drug antibodies may be neutralizing or non-neutralizing *in vitro*. However, even the non-neutralizing antibodies may adversely affect the pharmacokinetics (52).

Assessing for antibodies against therapeutic proteins may not reflect the full extent of immunogenicity, as measuring the magnitude of immunogenicity is extremely complex process affected by clinical, pharmacological, and immunological factors. Attempts to compare immunogenicity between agents and different studies are compromised by different trial designs, study populations, assay techniques, timing of measurements, route of drug administration, and potential effects of concomitant medication. Most available literature describes anti-drug antibodies assessed by enzyme immunoassays. These assays cannot detect all the different forms of antibodies, and they also differ significantly in specificity and sensitivity. Other problems are risk of false-positive reactions due to non-specific binding to immunoglobulins other than the drug, and inhibition of the assays by the presence of the drug in the serum because of drug–antibody complex formation. With the current available assays, free anti-drug antibodies are not detected if an excess of drug is present in the serum (24,26). Anti-drug antibodies are considered positive if the assay used detects antibody concentration above the cutoff value of the test and when it is associated with undetectable drug levels. Antibodies are considered negative if the assay used does not detect antibody concentration above the cutoff value of the test and concurrently does not detect any drug levels above the cutoff level of the test. An inconclusive antibody status is declared once an assay detects drug concentration above the cutoff value of the test in the absence of detectable anti-drug antibodies. Finally, it is not clear if enzyme immunoassays actually measure active anti-drug antibodies that truly interfere with the drug bioactivity. Noncommercial and more cumbersome assays such as radioimmunoassays surpass enzyme immunoassays in accuracy and also bear a functional advantage. Radioimmunoassays can measure the

binding capacity of TNFα with anti-TNFα and are less susceptible to artifact from other epitopes than TNFα. Moreover, such assays may reveal the presence of monovalent antibodies (IgG4) that would mostly go undetected by the current available enzyme immunoassays and may negatively impact anti-TNFα pharmacokinetics (56,57). It appears that radioimmunoassays better reflect the *in vivo* bioavailability with presumably lower false-positive rates. Gauging the binding capacity of TNFα in non-responders may assist in differentiating non-inflammatory states or alternative dominant inflammatory mechanism other than TNFα (high binding capacity and no anti-drug antibodies) from true immunogenicity with low TNFα-binding capacity and high anti-drug antibodies (40,41). Finally, although immunogenicity probably occurs to some extent in most patients treated with biologics, it appears to be relevant only when it alters the pharmacokinetics and impacts the clinical outcome.

The interpretation of antibody measurements should be linked to the timing of administration and dosing. To minimize the confounding presence of the drug in the serum, it is recommended to measure trough level, the serum drug concentration before the next infusion/injection. Trough level reflects the degree of the drug degradation. *In vitro* inhibition of TNFα is achieved with infliximab concentrations of 0.2–10 μg/ml (58); however, *in vivo* the optimal trough level, the lowest concentration sufficient to exert the full desired effect of the drug, is unknown. A *post hoc* analysis of rheumatoid arthritis (RA) patients from the ATTRACT study illustrated profound individual differences in infliximab trough levels, in spite of similar administration protocols contrasting allegedly predictable clearance rates. Correlation was demonstrated between infliximab levels and maintenance of response, irrespective of the mechanism responsible for the drug clearance. These results suggest that the trough level may be a relevant surrogate marker for bioactivity and that the drug dosing may need to be optimized on an individual basis. According to this study results, approximated optimal infliximab trough levels would be >10 μg/ml (59). Concordantly, a recent cross-sectional analysis with long-term follow-up of daily practice in RA confirmed these findings, and demonstrated that serum infliximab trough concentration of >1 mg/l predicts long-term low disease activity and that higher trough levels inversely correlates with disease activity markers (mostly with CRP) (60). Indeed, high infliximab serum concentrations and trough levels were consistently shown to be linked to higher response rates, higher remission rates, and longer duration of response both in CD and RA (25,26,41,54,59,61,62). As previously mentioned, anti-drug antibodies were initially considered primarily accountable for decreased serum drug levels and thus predictors of shorter duration of response (26,53). However, Maser *et al.* (25) demonstrated that trough levels are the actual predictors of response. This study clearly showed higher and longer clinical remission rates, higher endoscopic improvement rates, and lower CRP levels for patients with a detectable trough serum infliximab (categorized as inconclusive antibody status) compared with patients in whom serum infliximab was undetectable, including those with and without anti-drug antibodies (25). The same group also has demonstrated that, in moderately severe steroid-refractory UC patients, detectable infliximab trough levels, irrespective of anti-drug antibody status, are predictive of clinical response, endoscopic improvement, and lower colectomy rates (63). Furthermore, and consistent with findings from the analysis of the ACCENT I data, undetectable trough levels were reported in the absence of antibodies supporting the concept of alternative clearance mechanisms other than immunogenicity (25,55).

Favorable clinical outcomes are most likely the consequence of sustained serum therapeutic levels. Anti-drug antibodies are neither sufficient nor necessary for development of loss of response and altered pharmacokinetics. However, when anti-drug antibodies are present in the setup of loss of response, they may be a proxy for low trough levels driven, at least in part, by immunogenicity.

Unfortunately, commercial assays are not available for determination of adalimumab or certolizumab trough levels and antibody formation. Using their proprietary assay for adalimumab, Li *et al.* (64) were able to demonstrate a dose–exposure–response relationship for adalimumab in the CLASSIC I, but the overlap in serum concentrations within dose groups precluded the identification of a predictive trough concentration for treatment success/failure, and in the CLASSIC II maintenance study, serum concentrations of adalimumab did not consistently correlate with clinical remission status. However, as expected, Karmiris *et al.* (65) using an "in-house assay", demonstrated that adalimumab trough levels in 130 CD patients correlated with long-term clinical response, and antibodies against adalimumab had negatively affected trough levels. West *et al.* (27) reported that in a small cohort of CD patients, immunogenicity to adalimumab had a significant role in treatment failure. Coincidently, in RA patients, serum antibodies against adalimumab were shown to be neutralizing and associated with lower serum adalimumab concentrations and non-response (51,66). Discrepancies in these reports are likely due to different techniques and timing of assays, as well as the imprecision of clinical assessments correlating with inflammatory activity and markers (such as CRP).

Factors that would influence the formation of anti-drug antibodies are dose, dosing intervals, induction regimen followed by scheduled vs. episodic therapy (on demand), concomitant use of immunomodulators, and prophylactic steroids before infusion (26,53–55).

Data from subgroup analysis of clinical trials and prospective cohort studies have demonstrated that episodic administration of infliximab leads to significantly higher rates of ATIs than induction regimens followed by regularly scheduled maintenance therapy (up to 60% compared with <5%) (9,10,55,67). Recently, Lichtenstein *et al.* (17) presented the results of PRECiSE 3, an ongoing open-label study of maintenance therapy for CD patients with certolizumab pegol. Once again, this study showed a positive correlation between therapy interruption and development of antibodies to certolizumab and lower drug plasma levels (17). However, even scheduled regimens with anti-TNFα may not entirely halt the phenomenon of loss of response. Results of a long-term follow-up of infliximab therapy in CD patients demonstrated that despite scheduled maintenance therapy, up to 10% of

patients per year discontinue therapy because of loss of response or intolerance (68).

In contrast to the RA experience, *post hoc* analyses of phase III trials with infliximab, adalimumab, and certolizumab pegol failed to demonstrate synergism between immunomodulators and anti-TNFα in patients who were enrolled and already refractory to immunomodulator therapy (69–74). The benefit of concomitant use of immunomodulators with adalimumab or certolizumab pegol has not been established, although anti-drug antibody formation was decreased (14,16,18,19). Moreover, data from long-term "real-life" experience with adalimumab in CD has shown that combining immunomodulators with adalimumab at baseline does not influence trough levels, does not decrease antibody formation, or offer advantage on treatment outcome, and even corticosteroids at baseline had no correlation with sustained benefit (65). Data from ENACT-1 and ENACT-2 demonstrated that concomitant immunomodulators and corticosteroids were moderately protective against formation of antibodies to natalizumab (75).

Yet, it has been consistently shown that concomitant use of immunomodulator(s) reduces the neutralizing effect of anti-drug antibodies in the setting of episodic therapy. The impact of combination therapy with immunomodulators was first demonstrated in data from the ACCENT I and has been corroborated by several observational studies (25,26,53–55). Maser *et al.* (25) stratified CD patients treated with scheduled maintenance infliximab for the presence or absence of concomitant immunomodulators and observed that immunomodulators had a greater protective effect against the development of ATIs for those who were treated episodically, contrasting those who were treated with regular maintenance regimens. Correspondingly, Vermeire *et al.* (54) confirmed the efficacy of AZA and methotrexate in preventing ATI formation, infusion reactions, and improving the pharmacokinetic profile in episodically treated patients (44). Concordantly, from the "real-life" long-term experience with infliximab therapy in CD, a subgroup analysis based on immunomodulator use suggested that maximal benefit of concomitant immunomodulators occurred in the episodic infliximab group, as high-dose induction followed by maintenance therapy alone markedly reduced immunogenicity (68). In fact, Van Assche *et al.* (76) had shown no clinical advantage for continuing concomitant immunomodulators beyond 6 months in patients who maintained remission on combination therapy over scheduled infliximab monotherapy (most patients failed AZA before enrollment). There was no significant difference in ATI incidence in the two groups nonetheless; however, as the combined treatment approach resulted in sustained higher median infliximab trough levels, lower anti-drug titers, and lower CRP, it is predictable that there would be a continued decline in the proportion of patients who maintain longer-term responses (76).

In contrast, the SONIC trail, which enrolled immunomodulator- and biologic-naive patients, assessed the induction and maintenance of steroid-free remission by infliximab monotherapy, combination of infliximab and AZA, or AZA monotherapy. The results clearly demonstrate superiority for the combination therapy after 26 and 50 weeks of therapy. This benefit, at least in part, could be ascribed to suppression of immunogenicity and higher rates of detected infliximab trough levels (77).

Ultimately, there is no evidence to affirm that specific anti-TNFα antibodies cross-react with a different anti-TNFα agent, and therefore the presence of anti-drug antibodies does not preclude switching to another anti-TNFα within the same class (57,65,78).

REVIEW

APPROACH TO PRIMARY NON-RESPONSE AND LOSS OF RESPONSE

Strategies to optimize response to anti-TNFα agents

Foremost, because of the current positioning of biological agents for patients refractory to conventional therapies, the paucity of subsequent alternative medical approaches, and the substantial cost of biological therapy, clinicians should make any effort to avoid loss of response. This is best achieved by properly selecting patients who may benefit most from therapy. Patients with non-inflammatory symptoms or those with symptomatic stenosis are least likely to respond. High-dose induction therapy, followed by regularly scheduled maintenance rather than episodic (p.r.n.) therapy, is recommended with all biologics in order to sustain therapeutic levels, avoid immunogenicity, and improve clinical outcomes. With infliximab, in situations in which there has been a hiatus in treatment or if the patient has been treated on an episodic basis, concomitant immunomodulators and prophylactic steroids can decrease the incidence of antibody formation and thus prevent infusion reactions and secondary loss of response (25,26,54). Although, *post hoc* analyses of trials with infliximab, adalimumab, and certolizumab pegol, enrolling patients with refractory CD despite immunomodulatory therapy, did not demonstrate clinical benefits from combination therapy, the prospective SONIC trial clearly demonstrated a benefit of combination therapy for patients with earlier disease who were naive to both immunomodulatory and biological therapy.

Suggested management of primary non-response to anti-TNFα agents

Optimal treatment strategies have yet to be defined for patients who are primary non-responders to an anti-TNFα agent. Unfortunately, clinical trials of newer anti-TNFα agents have thus far excluded patients who were primary non-responders to another anti-TNFα agent. Only a few small, uncontrolled studies have evaluated the efficacy of secondary anti-TNFα therapy in primary non-responders with CD. One study included four infliximab primary non-responders, one of whom responded to adalimumab (79). Another study included six infliximab primary non-responders, five of whom had colonic CD. Three of the six responded to adalimumab (80). Recently, Danese *et al.* (81) reported successful induction of response and remission by certolizumab pegol in a small cohort of CD patients who were primary non-responders to infliximab. Regrettably, even the rheumatological experience does not offer satisfactory scientific resolution for this issue. RCTs and head-to-head trials comparing different therapeutic strategies in primary non-responders are lacking, and the few observational studies in RA addressing this issue clearly demonstrate that the

majority of patients do not achieve an ACR50 response when switched to an alternative anti-TNFα. Available small head-to-head studies in RA patients indicate that switching across classes (rituximab) may surpass switching within class (an alternative anti-TNFα) (82).

In view of the lack of substantial evidence-based algorithms, we endorse the following strategy. We recommend that after 4–12 weeks of therapy, depending on agent and dosing, primary non-responders be re-evaluated for non-inflammatory symptoms and for determining the disease extent. Surgical resection may be an option for patients with limited disease extent and, of course, colectomy needs to be considered when dealing with UC. For CD patients who have failed conventional agents, therapy with natalizumab, which has demonstrated efficacy for CD patients who failed anti-TNFα, may be considered (83). Although there is no substantial guidance regarding primary failures to adalimumab and certolizuimab pegol, due to the relative increased dosing for infliximab, we would consider a trial of infliximab for primary non-responders. In contrast, the literature is less optimistic regarding treatment of primary non-responders to infliximab who were subsequently treated with the injectable anti-TNFα formulations. Unfortunately, at present, revisiting the experience, reviewing optimization of conventional agents, and consideration for clinical trials are some of the limited options for the setting of most primary non-responders to anti-TNFα biologics.

Suggested management of secondary non-response to anti-TNFα agents

Patients who lose response should always be reassessed in order to evaluate disease activity aside from symptoms. Inflammatory biomarkers such as CRP and fecal calprotectin should be measured and either endoscopic or dedicated imaging must be performed to exclude non-inflammatory explanations for symptoms. Once inflammation is confirmed, assessing for altered pharmacokinetics and potential immunogenicity may impact and direct treatment decisions.

When assessing loss of response to infliximab, a useful approach would be to measure infliximab levels at 4 weeks after an infusion (26,54) or trough levels, the drug concentration just before the next infusion (25). Infliximab concentrations ≥12 μg/ml at 4 weeks after an infusion are considered therapeutic and highly correlated with longer duration of response and lower levels of ATI (26). The Mayo Clinic group has demonstrated the utility of combining infliximab levels and determination of ATI in the clinical management of patients who lose response to infliximab (84). If trough levels are low or undetected, proceeding with anti-drug antibody levels may differentiate immunogenicity from individual rapid drug elimination and direct with the preferred management (dose intensification vs. switching). Patients who lose response to infliximab associated with anti-infliximab antibodies respond well to switching to adalimumab or certolizumab pegol. Conversely, detecting therapeutic drug levels without anti-drug antibodies in a patient who had lost response may still be due to inability to exclude low titers of anti-drug antibodies (because of limitations of the assay to identify antibodies in the presence of free drug). Nevertheless, patients with adequate blood levels are unlikely to respond to an alternative formulation with the same mechanism of action, as this likely represents failure of the drug to control inflammation (presumably because of a different dominant mechanism that drives inflammation, a pharmacodynamic setback). Even if immunogenicity still exists, detectable infliximab implies antibody saturation, and therefore not expected to hamper the drug pharmacokinetics. As aforementioned, Maser *et al.* (25) found that the subgroup of patients who were inconclusive for anti-drug status had better clinical outcome compared with those who were anti-drug positive or anti-drug negative. This favorable outcome was attributed to sustained drug concentrations in the inconclusive antibody subgroup. Of note, the same auspicious findings were shown in the inconclusive antibody subgroup from the ACCENT I trial; moreover, only 2.5% of those patients were proved to be antibody positive at 26 weeks after their last infusion (55). Hence, when losing response with evident trough levels, a practical approach would be to switch therapy across classes.

Again, for patients who lose response to adalimumab or certolizumab pegol, commercial assays are not available and assessments for mechanisms of loss of response need to be clinical. A simple question directed to all of our patients on maintenance biological therapy is whether they feel different throughout the dosing cycle. If patients improve with each treatment, but develop increasing symptoms that are alleviated with the next dose, it can be inferred that the dose or dosing interval should be adjusted. However, if the patient loses response and fails to attain any benefit from a subsequent infusion or injection, it is unlikely that administration of a higher dose or shorter interval between doses will provide any benefit.

Stemming from practice experience, in the majority of patients, response can be restored by dose and interval adjustments (65,68), and perhaps this strategy yields more quality-adjusted life compared with switching (although at a considerable cost) (85). Response may be recaptured with subsequent dosing, and is a particularly useful strategy when the drug trough levels (if can be measured) are sub-therapeutic and there is no significant anti-drug antibody formation (25,26,41,59). Either increasing doses and/or decreasing intervals between doses are relevant options. Studies in IBD and in RA demonstrated advantage in sustained therapeutic plasma drug levels in order to maintain response (25,59). In maintenance trials with infliximab and adalimumab, significant percentages of patients required increased doses (infliximab) and or decreased treatment intervals (adalimumab) in order to restore response after interval symptoms developed between dosing (9,10,14,19). Analysis of the data from the ACCENT I trial demonstrated that amongst a subgroup of patients who lost response to 5 mg/kg scheduled infliximab infusions, 90% successfully regained response after receiving a 10 mg/kg dose (67). Similarly, preliminary results from PRECiSE 4 support the potential for recapturing responses with certolizumab pegol with incremental dosing adjustments (86). Pharmacokinetic models of infliximab in RA indicate that higher trough concentration may be achieved by shortening the interval or dose escalation, with a relative advantage for the shortening interval approach (59). Data from a "real-life" cohort

of CD patients treated with infliximab demonstrates that 50% of the primarily responsive patients needed at least one intervention, that is, dose escalation, shortened interval, re-induction, or a combination of two interventions. Those interventions were succsessful in achieving maintained remission in approximatly half of the patients. Nevertheless, from the same data it appears that even after scheduled maintenance therapy and dose adjustments, substantial numbers of patients will still lose response (68). The same group reported that in a cohort of CD patients treated with adalimumab, loading regimen and dose escalation were shown to have the most significant impact on long-term response. Of the initial responders, 65% (102/156) needed dose escalation, which appeared successful in ~70%, and the probability for dose escalation throughout time was ~80% at 120 weeks (65). As mentioned above, a single-center retrospective study from the Mayo Clinic demonstrated the utility and impact of measuring infliximab levels and in routine practice for 155 IBD patients who had inadequate response or intolerance to infliximab. The test results impacted treatment decisions in 73% of the cases. Patients who were found with sub-therapeutic drug levels benefited more from dose escalation compared with switching therapy (86 vs. 33% patients improved, respectively). However, patients who lost response with evident positive human anti-chimeric antibodies significantly benefited from switching to an alternative anti-TNFα compared with dose escalation (91 vs. 16% patients improved, respectively) (84).

Switching between biologics is an important strategy for patients who lose response because of immunogenicity followed by rapid drug clearance or when a significant alternative pathogenic role is suspected. Switching can be within class or with an alternative class. Such "switching" strategies have been similarly implemented in other immune-mediated inflammatory disorders such as RA.

Switching from one anti-TNFα agent to a second (or even third) has emerged as a way to manage treatment in RA failures and has proven effective. The usefulness of this strategy was corroborated by several observational and retrospective studies. However, it seems that the efficacy of successive agents is decreased compared with the primary agent, as manifested by shorter "drug survival." In addition, it appears that patients who lose response to a first agent are more likely to lose response to a second and, similarly, those with toxicity to a first agent are more likely to develop toxicity from a second anti-TNFα agent. This diminishing outcome may, in part, be due to a class effect and possibly secondary to selection bias toward switching in those who have greater disease burden or "refractoriness" (82). Alternatively, this can be explained by the versatility of biologics in terms of function even within the same class of drugs. These differences could be attributed to differences in structure, pharmacokinetics, different subtle mechanisms of action, the mode of administration, diverse complex pathogenesis of the immune-mediated diseases, and different genetic makeup of individual patients. The phenomenon of anti-TNFα agents promoting paradoxical autoimmune reactions such as lupus-like reactions, skin eruptions, eczema-like manifestations, and psoriasiform lesions in various immune-mediated conditions illustrates this point (28,87). Of note, etanercept, which is an anti-TNFα approved for RA and other spondyloarthropathies (but lacks efficacy for CD), was found to be associated with promotion of *de novo* cases of IBD, especially in ankylosing spondylitis (88).

Ultimately, switching between different classes has become an accepted standard of care in RA. Rituximab (anti-CD20 monoclonal antibody) and abatacept (anti-CD80/anti-CD86 fusion protein), two alternative biologics with novel mechanism of action, were recently approved for patients with primary and secondary anti-TNFα failure (89,90). A small observational study that compared switching with a second anti-TNFα vs. rituximab ("head-to-head" comparison) demonstrated the superiority of rituximab (91). Interestingly, an extended analysis of more than 300 patients by the same group confirmed these results and also showed that rituximab is more effective in patients who stopped a previous anti-TNFα therapy because of ineffectiveness, as opposed to adverse effects (92).

In CD, an open-label phase II study of 24 patients who lost response or were intolerant to infliximab demonstrated that adalimumab was safe and potentially effective alternative (93). Subsequently, the GAIN trial was the first RCT to assess the efficacy of a second anti-TNFα therapy in an immune-mediated disease. Previously, anti-TNFα-treated CD patients who had developed intolerance or loss of response to infliximab and presented with moderate-to-severe disease activity (CDAI 220–450) were randomized to adalimumab or placebo. At week 4, the rates of clinical remission in the adalimumab- and placebo-treated groups were 21.4 and 7.2%, respectively ($P=0.0006$). In contrast with the emerging data from RA, this study showed no difference in remission rates between subgroups of patients who entered the trial because of loss of response or intolerance to infliximab. Although statistically significant, the demonstrated response rates were lower compared with those seen in the CLASSIC I trial (a pivotal study for induction therapy with adalimumab in CD) (20). The CHARM trial, a RCT that assessed adalimumab for maintenance therapy in CD, included a subgroup of patients who had been previously exposed to infliximab. At week 56, both groups demonstrated superior benefits over placebo, but concordant with the RA data, the absolute remission rates for anti-TNFα-naive patients were greater than for those who had been previously exposed to infliximab (48 vs. 34%) (14). The PRECiSE 1 trial, a randomized placebo-controlled evaluation of certolizumab pegol as induction therapy for patients with moderate-to-severe CD also enrolled both infliximab-naive and experienced patients. Of the 28% of subjects with a previous exposure to infliximab, mostly with loss of response, there was no benefit for the infliximab-exposed group compared with placebo (18). The PRECiSE 2 trial that evaluated the efficacy of certolizumab pegol to maintain remission among responders also enrolled a subgroup (24% of the patients) that had been previously exposed to infliximab. Notwithstanding, certolizumab pegol was more effective than placebo at maintaining remission in the study population as a whole and in the subpopulation previously exposed to infliximab; the relapse rate at 26 weeks was substantially higher in infliximab-exposed patients (21).

Assimilating data from RCTs in IBD and the data from RA studies suggest that patients who have received infliximab in previous treatments will have, on average, an 8–15% reduction

in clinical efficacy when treated with a second anti-TNFα agent. This may be secondary to increasing duration of disease and progressive structural damage, an increased likelihood of developing immunogenicity to a second (or third) biologic, an individual's inherent increase in drug metabolism, or to loss of response to anti-TNFα mechanism.

Most open-label studies and small cohorts of patients demonstrate relatively better results with switching to anti-TNFα therapy than RCTs. Vermeire *et al.* (94) presented the results of an open-label phase IIIb multicentre study of the WELCOME trial with certolizumab pegol. In this study, 582 patients who were intolerant to or had secondary loss of response to infliximab, received induction dosing with certolizumab pegol. At week 6, 61% of the patients had achieved the primary end point of response, and 39% of the patients were in remission (94). Panaccione *et al.* (95) presented the results of a *post hoc* analysis of 1-year open-label follow-up extension of the GAIN trial. This study demonstrated sustained efficacy for adalimumab in maintaining clinical remission and response in patients who failed previous infliximab therapy (95). A small cohort of 53 CD patients from France demonstrated significant, long-lasting (130 weeks) efficacy for adalimumab as a second-line therapy for CD patients who lost response to infliximab (96). Karmiris *et al.* (65) reported results of a long-term experience of 168 CD patients who previously failed to respond (68%) or were intolerant (32%) to infliximab and switched to adalimumab. Of the initial responders, 61% (96/156) had sustained clinical response during a median follow-up of 20 months. The probability of maintaining sustained response was ~50% at 120 weeks and 38% at 180 weeks. Interestingly, the presence of human anti-chimeric antibody before initiation of adalimumab was not associated with increased incidence of antibodies against adalimumab (65). Lichtiger *et al.* (97) presented the results of CHOICE, a US-based, multicenter, open-label trial that enrolled 673 patients with moderately severely active CD who were primary and secondary non-responders to infliximab or became intolerant. Patients received induction and maintenance adalimumab and, after 8 weeks, the adalimumab interval dosing was adjusted according to response. Quality of life according to the short form of the inflammatory bowel disease questionnaire (IBDQ) was assessed at weeks 4, 8, 12, and 24, and demonstrated significant improvement in scores at all scheduled visits, with greatest impact at week 24 (97). Another small cohort of CD patients demonstrated the efficacy of a third anti-TNFα monoclonal antibody after failure of two other anti-TNFα therapies. This open-label study showed that 41 out of 67 patients (61%) who had received adalimumab or certolizumab pegol as a third anti-TNFα therapy had evidence of clinical response at 6 weeks, and that 34 patients (51%) had maintained response at 20 weeks (98).

Finally, West *et al.* (27) demonstrated high response rates for adalimumab in a small group of CD patients who previously failed infliximab therapy. In that small cohort, a subgroup of five patients (17%) demonstrated immunogenicity to adalimumab that was associated with adalimumab failure. Of note, ATIs were found in 57% of this cohort; however, significantly increased ATI levels were found only in the patients who failed adalimumab. The investigators in this study speculated that previous infliximab therapy might be an important immunizing factor that predisposes for immunogenicity to adalimumab (27). These findings are discrepant with the results of the GAIN study, the results of its extension of 1-year follow-up (20,95), and the findings reported by Karmiris *et al.* (65). Although comparing the rate of anti-adalimumab antibodies between different studies is impractical because of lack of standardization of assays, antibody formation could be, at least in part, the reason for reduced efficacy when treated with a second anti-TNFα agent.

Switching anti-TNFα agent with a biologic that has an alternative mechanism of action, such as natalizumab, or with newer investigational drugs is an option for CD patients who expressed non-response or loss of response to anti-TNFα therapy. The ENACT-1 study was performed to assess induction of response to natalizumab. A total of 40% of the enrolled patients had previously received anti-TNFα therapy. Although the primary end point in ENACT-1 failed to show a benefit for natalizumab induction in CD, the subgroups of patients who received natalizumab with previous anti-TNFα exposure had better response compared with placebo (55 vs. 35%, respectively, $P<0.05$). Subjects who had a response to induction therapy in ENACT-1 were enrolled in ENACT-2 to assess maintenance benefits of natalizumab. The study showed that natalizumab was superior to placebo in maintaining response, including in patients previously exposed to anti-TNFα therapy (43 vs. 11%) (75). *Post hoc* analysis of ENCORE (a different phase III induction study) and the ENACT-2 demonstrated that administration of natalizumab in infliximab failures, who were not receiving concomitant immunomodulators, had significant better response and remission rates compared with placebo (99). As presented previously, in the rheumatology literature, switching to a different class might be preferred when loss of response is not secondary to adverse events or immunogenicity (presumably suggestive of a different dominant immunoinflammatory mechanism other than TNFα).

In summary, the practicalities of determining the cause for secondary loss of response are substantial. According to the presented data, we have designed an algorithm that may prove to be useful in assessing and managing loss of response (**Figure 1**). Nevertheless, the management of patients on biologics, who lose response and have evident active inflammation, is mostly empirical. In daily practice, stratifying CD (and presumably UC) patients according to the pattern of loss of response serves in directing the clinical approach; substantial but suboptimal response would be addressed with dose escalation, gradual loss throughout the dosing cycle would be addressed with increasing doses or decreased intervals, and lack of response to subsequent infusions/injections would be addressed by switching to an alternative anti-TNFα therapy. When feasible, measuring drug levels and anti-drug antibodies may be of great benefit in optimizing therapy. Patients who lose response to a biologic because of low drug trough levels without anti-drug antibodies may respond to drug intensification (increased dose or decreased intervals between doses). Patients who lose response to a biologic because of immunogenicity, low drug trough levels with high anti-drug antibodies, are most likely to respond to a second

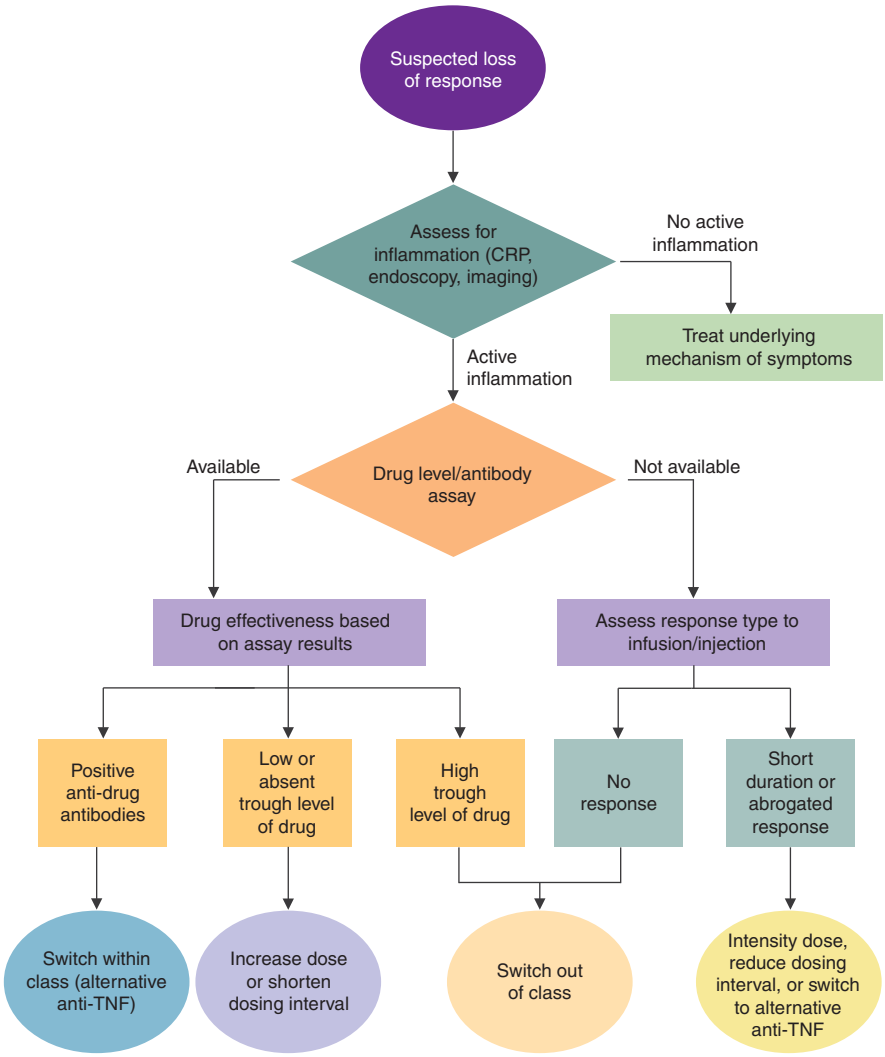

Figure 1. Suggested clinical approach to loss of response to anti-tumor necrosis factor-α (anti-TNFα) therapy. CRP, C reactive protein.

agent within the same class (presumably both UC and CD patients, although there is only evidence, to date, in the setting of CD). Then again, once antibodies are present (even in low titers), prophylaxis with hydrocortisone and possibly (re)starting an immunomodulator combined with dose adjustments may be considered conjointly with dose adjustments. Eventually, using the current available assays for measuring immunogenicity might be inconclusive for patients who lose response with measurable circulating drug but without anti-drug antibodies. Such patients may still suffer from immunogenicity (undetectable) and may benefit from a second anti-TNFα therapy; however, they are more likely to profit from switching to a medication with a different mechanism of action (an alternative class). Patients classified as having lost response to a biologic because of intolerance (acute or delayed infusion reactions or injection site reactions that are usually associated with immunogenicity) will also, typically, respond to a second agent within class. Although one would assume that these recommendations will also apply to UC patients on the basis of data with adalimumab (100), colectomy remains an option for individuals who fail to respond or lose response to biologics targeting TNFα (101).

In the future, we envision individualized therapy for IBD patients treated with biologics based on advanced phenotyping, pharmacogenomics, and pharmacokinetics. We have noted the need for dose adjustments in nearly half of our patients during maintenance therapy, but unfortunately, standardized assays that have been reproduced and validated according to elimination of inflammatory activity are not uniformly available. It is also quite possible that requisite serum levels may raise or fall during the course of disease according to the "inflammatory burden." Nevertheless, at present, we are unable to propose or predict individualized dosing or a scaled order for choosing between agents until well-designed, targeted, and comparative effectiveness research addresses these pertinent issues. Furthermore, it has not been evaluated whether the benefits of combination therapy are related solely to increase in serum levels (for example, SONIC) or due to combined mechanisms of action, and also whether the benefit of combination

therapy will be demonstrable across biological agents (with different patterns of immunogenicity) or apply to all subgroup(s) of patients. Thus, atpresent, we must rely on clinical symptoms, signs and endoscopic responses, and generic biomarkers (CRP, fecal calprotectin) to assess individual patient responses and to correlate with dosing strategies.

DISCUSSION

The two cases presented are illustrations of common clinical scenarios requiring evidence-based management and risk stratification. The first step in managing all clinical cases of nonresponse or loss of response is the assessment and confirmation of active inflammatory disease while excluding potential pitfalls (**Figure 1**).

The first case presents a 28-year-old male with a long history of CD, who was previously maintained on an adequate dose of 6-mercaptopurine for years. The patient presented with severe exacerbation after failing a course of steroids. Active inflammation was suggested by the elevated CRP, conformation and extent evaluation was completed by colonoscopy and computed tomography enterography. Infliximab was initiated as salvage treatment, but the patient failed the induction (two infusions). This is an example of primary non-response. Inflammation was established and a mechanical reason for failure was ruled out with an appropriate dedicated imaging study (conventional barium, computed tomography, or MR enterography). A possible reason for failure in this case may be an alternative dominant immunoinflammatory mechanism other than TNFα. Reviewing the patient's previous medical history revealed that he had already failed 6-mercaptopurine that was optimally dosed. The option of methotrexate was not pertinent, as the patient was not responding to steroids, while it is expected that methotrexate will present beneficial effect only several weeks after initiation. Hence, a trial with a biological agent from a different class, natalizumab, was offered (**Figure 1**). The other relevant option in this case was surgery, resecting the affected inflamed distal ileum (a relative short segment).

The second case presents a 29-year-old female with a long history of ileocolonic disease, who maintained a reasonable remission for several years on a combination of AZA and sulfasalazine. Two years before her current presentation, the patient relapsed and therapy with infliximab was initiated. She responded and maintained in remission with scheduled infliximab therapy in combination with AZA. Over time, her response faded and her symptoms recurred. The patient's therapy was adjusted, first by decreasing the interval of infusions and later by increasing the dose. Nevertheless, with time, the patient had presented with active inflammation established by colonoscopy, accompanied by non-detectable infliximab levels with evident ATI, suggesting immunogenicity. This case presents an example of secondary loss of response. Optimization of therapy was attempted by using infliximab in conjunction with the AZA in a scheduled manner in order to minimize the likelihood for immunogenicity. However, in spite of therapy optimization, the patient eventually developed immunogenicity and lost response. Using the commercially available assay enabled corroborating immunogenicity and directing management toward switching within class. The patient therapy was successfully switched to adalimumab induction and maintenance therapy.

CONCLUSION

Biologics have contributed significantly to the conventional arsenal of treatments for IBD, offering the ability to induce and maintain remission, heal mucosa, restore quality of life, and reduce surgeries and hospitalizations. Yet, a significant proportion of patients will not respond or will lose response. It is essential to recognize the spectrum of mechanisms affecting response and loss of response in order to form a logical and efficient management algorithm, and perhaps it is time to incorporate the measurement of trough levels and anti-drug antibodies in the strategy of such an assessment.

The current literature supports a practice of dose adjustments and switching biologics, although efficacy is reduced with second-line agents either within or across classes compared with naive patients. In the absence of direct measurement of drug levels and anti-drug antibodies, clinical judgment is necessary to assess the mechanisms of loss of response, and more empiric decision making may be necessary to determine the choice of second-line biological agents. Prospective controlled trials are direly needed to investigate the optimal tailored management in individual patients who lose response.

CONFLICT OF INTEREST

Guarantors of the article: Henit Yanai, MD and Stephen B. Hanauer, MD.

Specific author contributions: Henit Yanai and Stephen B. Hanauer conceived the review, collected the data, and drafted the manuscript.

Financial support: None.

Potential competing interests: Stephen B. Hanauer has received institutional clinical research support from Abbott, Centocor, and UCB. He has also provided consulting and advisory board services to Abbott, Centocor, and UCB.

REFERENCES

1. Bamias G, Nyce MR, De La Rue SA *et al.* New concepts in the pathophysiology of inflammatory bowel disease. Ann Intern Med 2005;143:895–904.
2. Baumgart DC, Carding SR. Inflammatory bowel disease: cause and immunobiology. Lancet 2007;369:1627–40.
3. Cho JH, Weaver CT. The genetics of inflammatory bowel disease. Gastroenterology 2007;133:1327–39.
4. Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. Nature 2007;448:427–34.
5. Wong M, Ziring D, Korin Y *et al.* TNFalpha blockade in human diseases: mechanisms and future directions. Clin Immunol 2008;126:121–36.
6. Braegger CP, Nicholls S, Murch SH *et al.* Tumour necrosis factor alpha in stool as a marker of intestinal inflammation. Lancet 1992;339:89–91.
7. MacDonald TT, Hutchings P, Choy MY *et al.* Tumour necrosis factor-alpha and interferon-gamma production measured at the single cell level in normal and inflamed human intestine. Clin Exp Immunol 1990;81:301–5.
8. Schreiber S, Nikolaus S, Hampe J *et al.* Tumour necrosis factor alpha and interleukin 1beta in relapse of Crohn's disease. Lancet 1999;353:459–61.
9. Hanauer SB, Feagan BG, Lichtenstein GR *et al.* Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359:1541–9.
10. Sands BE, Anderson FH, Bernstein CN *et al.* Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med 2004;350:876–85.

11. Targan SR, Hanauer SB, van Deventer SJ *et al.* A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med 1997;337:1029–35.
12. Clark M, Colombel JF, Feagan BC *et al.* American gastroenterological association consensus development conference on the use of biologics in the treatment of inflammatory bowel disease, June 21–23, 2006. Gastroenterology 2007;133:312–39.
13. Lichtenstein GR, Bala M, Han C *et al.* Infliximab improves quality of life in patients with Crohn's disease. Inflamm Bowel Dis 2002;8:237–43.
14. Colombel JF, Sandborn WJ, Rutgeerts P *et al.* Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007;132:52–65.
15. Colombel JF, Schwartz DA, Sandborn WJ *et al.* Adalimumab for the treatment of fistulas in patients with Crohn's disease. Gut 2009;58:940–8.
16. Hanauer SB, Sandborn WJ, Rutgeerts P *et al.* Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology 2006;130:323–33; quiz 591.
17. Lichtenstein GR, Thomsen OO, Schreiber S *et al.* Continuous therapy with certolizumab pegol maintains remission of patients with Crohn's disease for up to 18 months. Clin Gastroenterol Hepatol 2010;8:600–9.
18. Sandborn WJ, Feagan BG, Stoinov S *et al.* Certolizumab pegol for the treatment of Crohn's disease. N Engl J Med 2007;357:228–38.
19. Sandborn WJ, Hanauer SB, Rutgeerts P *et al.* Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut 2007;56: 1232–9.
20. Sandborn WJ, Rutgeerts P, Enns R *et al.* Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. Ann Intern Med 2007;146:829–38.
21. Schreiber S, Khaliq-Kareemi M, Lawrance IC *et al.* Maintenance therapy with certolizumab pegol for Crohn's disease. N Engl J Med 2007;357:239–50.
22. Schreiber S, Rutgeerts P, Fedorak RN *et al.* A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. Gastroenterology 2005;129:807–18.
23. Sandborn WJ, Hanauer SB, Katz S *et al.* Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. Gastroenterology 2001;121:1088–94.
24. Wolbink GJ, Aarden LA, Dijkmans BA. Dealing with immunogenicity of biologicals: assessment and clinical relevance. Curr Opin Rheumatol 2009;21:211–5.
25. Maser EA, Villela R, Silverberg MS *et al.* Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. Clin Gastroenterol Hepatol 2006;4:1248–54.
26. Baert F, Noman M, Vermeire S *et al.* Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med 2003;348:601–8.
27. West RL, Zelinkova Z, Wolbink GJ *et al.* Immunogenicity negatively influences the outcome of adalimumab treatment in Crohn's disease. Aliment Pharmacol Ther 2008;28:1122–6.
28. Fidder H, Schnitzler F, Ferrante M *et al.* Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study. Gut 2009;58:501–8.
29. Lichtenstein GR, Feagan BG, Cohen RD *et al.* Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. Clin Gastroenterol Hepatol 2006;4:621–30.
30. Toruner M, Loftus EV Jr, Harmsen WS *et al.* Risk factors for opportunistic infections in patients with inflammatory bowel disease. Gastroenterology 2008;134:929–36.
31. Siegel CA, Marden SM, Persing SM *et al.* Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. Clin Gastroenterol Hepatol 2009;7:874–81.
32. Mackey AC, Green L, Liang LC *et al.* Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2007;44:265–7.
33. Shale M, Kanfer E, Panaccione R *et al.* Hepatosplenic T cell lymphoma in inflammatory bowel disease. Gut 2008;57:1639–41.
34. Rutgeerts P, Sandborn WJ, Feagan BG *et al.* Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353:2462–76.
35. Ghosh S. Therapeutic value of alpha-4 integrin blockade in inflammatory bowel disease: the role of natalizumab. Expert Opin Biol Ther 2003;3: 995–1000.
36. Ghosh S, Goldin E, Gordon FH *et al.* Natalizumab for active Crohn's disease. N Engl J Med 2003;348:24–32.
37. Yousry TA, Major EO, Ryschkewitsch C *et al.* Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. N Engl J Med 2006;354:924–33.
38. Vermeire S, van Assche G, Rutgeerts P. Review article: altering the natural history of Crohn's disease—evidence for and against current therapies. Aliment Pharmacol Ther 2007;25:3–12.
39. D'Haens GR, Fedorak R, Lemann M *et al.* Endpoints for clinical trials evaluating disease modification and structural damage in adults with Crohn's disease. Inflamm Bowel Dis 2009;15:1599–604.
40. Bendtzen K, Geborek P, Svenson M *et al.* Individualized monitoring of drug bioavailability and immunogenicity in rheumatoid arthritis patients treated with the tumor necrosis factor alpha inhibitor infliximab. Arthritis Rheum 2006;54:3782–9.
41. Ainsworth MA, Bendtzen K, Brynskov J. Tumor necrosis factor-alpha binding capacity and anti-infliximab antibodies measured by fluid-phase radioimmunoassays as predictors of clinical efficacy of infliximab in Crohn's disease. Am J Gastroenterol 2008;103:944–8.
42. Ebert EC, Das KM, Mehta V *et al.* Non-response to infliximab may be due to innate neutralizing anti-tumour necrosis factor-alpha antibodies. Clin Exp Immunol 2008;154:325–31.
43. Cosnes J, Cattan S, Blain A *et al.* Long-term evolution of disease behavior of Crohn's disease. Inflamm Bowel Dis 2002;8:244–50.
44. Lionetti P, Bronzini F, Salvestrini C *et al.* Response to infliximab is related to disease duration in paediatric Crohn's disease. Aliment Pharmacol Ther 2003;18:425–31.
45. Kugathasan S, Werlin SL, Martinez A *et al.* Prolonged duration of response to infliximab in early but not late pediatric Crohn's disease. Am J Gastroenterol 2000;95:3189–94.
46. Hyams J, Crandall W, Kugathasan S *et al.* Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology 2007;132:863–73; quiz 1165–6.
47. Louis EJ, Watier HE, Schreiber S *et al.* Polymorphism in IgG Fc receptor gene FCGR3A and response to infliximab in Crohn's disease: a subanalysis of the ACCENT I study. Pharmacogenet Genomics 2006;16:911–4.
48. Louis E, El Ghoul Z, Vermeire S *et al.* Association between polymorphism in IgG Fc receptor IIIa coding gene and biological response to infliximab in Crohn's disease. Aliment Pharmacol Ther 2004;19:511–9.
49. Arijs I, Li K, Toedter G *et al.* Mucosal gene signatures to predict response to infliximab in patients with ulcerative colitis. Gut 2009;58:1612–9.
50. Hlavaty T, Pierik M, Henckaerts L *et al.* Polymorphisms in apoptosis genes predict response to infliximab therapy in luminal and fistulizing Crohn's disease. Aliment Pharmacol Ther 2005;22:613–26.
51. Bartelds GM, Wijbrandts CA, Nurmohamed MT *et al.* Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. Ann Rheum Dis 2007;66:921–6.
52. Lobo ED, Hansen RJ, Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. J Pharm Sci 2004;93:2645–68.
53. Farrell RJ, Alsahli M, Jeen YT *et al.* Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: a randomized controlled trial. Gastroenterology 2003;124:917–24.
54. Vermeire S, Noman M, Van Assche G *et al.* Effectiveness of concomitant immunosuppressive therapy in suppressing the formation of antibodies to infliximab in Crohn's disease. Gut 2007;56:1226–31.
55. Hanauer SB, Wagner CL, Bala M *et al.* Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. Clin Gastroenterol Hepatol 2004;2:542–53.
56. Bendtzen K, Ainsworth M, Steenholdt C *et al.* Individual medicine in inflammatory bowel disease: monitoring bioavailability, pharmacokinetics and immunogenicity of anti-tumour necrosis factor-alpha antibodies. Scand J Gastroenterol 2009;44:1–8.
57. Svenson M, Geborek P, Saxne T *et al.* Monitoring patients treated with anti-TNF-alpha biopharmaceuticals: assessing serum infliximab and anti-infliximab antibodies. Rheumatology (Oxford) 2007;46:1828–34.
58. Knight DM, Trinh H, Le J *et al.* Construction and initial characterization of a mouse-human chimeric anti-TNF antibody. Mol Immunol 1993;30 :1443–53.
59. St Clair EW, Wagner CL, Fasanmade AA *et al.* The relationship of serum infliximab concentrations to clinical improvement in rheumatoid arthritis: results from ATTRACT, a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002;46:1451–9.
60. Mulleman D, Chu Miow Lin D, Ducourau E *et al.* Trough infliximab concentrations predict efficacy and sustained control of disease activity in rheumatoid arthritis. Ther Drug Monit 2010;32:232–6.

61. Mori S. A relationship between pharmacokinetics (PK) and the efficacy of infliximab for patients with rheumatoid arthritis: characterization of infliximab-resistant cases and PK-based modified therapy. Mod Rheumatol 2007;17:83–91.
62. Wolbink GJ, Voskuyl AE, Lems WF *et al.* Relationship between serum trough infliximab levels, pretreatment C reactive protein levels, and clinical response to infliximab treatment in patients with rheumatoid arthritis. Ann Rheum Dis 2005;64:704–7.
63. Seow CH, Newman A, Irwin SP *et al.* Trough serum infliximab: a predictive factor of clinical outcome for infliximab treatment in acute ulcerative colitis. Gut 2010;59:49–54.
64. Li J, Paulson S, Chiu Y *et al.* Evaluation of potential correlations between serum adalimumab concentration and remission in patients with Crohn's disease in classic I and II. Gastroenterology 2010;138:741.
65. Karmiris K, Paintaud G, Noman M *et al.* Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. Gastroenterology 2009;137:1628–40.
66. Radstake TR, Svenson M, Eijsbouts AM *et al.* Formation of antibodies against infliximab and adalimumab strongly correlates with functional drug levels and clinical responses in rheumatoid arthritis. Ann Rheum Dis 2009;68:1739–45.
67. Rutgeerts P, Feagan BG, Lichtenstein GR *et al.* Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology 2004;126:402–13.
68. Schnitzler F, Fidder H, Ferrante M *et al.* Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. Gut 2009;58:492–500.
69. Furst DE, Schiff MH, Fleischmann RM *et al.* Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol 2003;30:2563–71.
70. Keystone EC, Kavanaugh AF, Sharp JT *et al.* Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum 2004;50:1400–11.
71. Lipsky PE, van der Heijde DM, St Clair EW *et al.* Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med 2000;343:1594–602.
72. Maini R, St Clair EW, Breedveld F *et al.* Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999;354:1932–9.
73. Weinblatt ME, Keystone EC, Furst DE *et al.* Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum 2003;48:35–45.
74. Weisman MH, Moreland LW, Furst DE *et al.* Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study. Clin Ther 2003;25:1700–21.
75. Sandborn WJ, Colombel JF, Enns R *et al.* Natalizumab induction and maintenance therapy for Crohn's disease. N Engl J Med 2005;353:1912–25.
76. Van Assche G, Magdelaine-Beuzelin C, D'Haens G *et al.* Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: a randomized trial. Gastroenterology 2008;134:1861–8.
77. Sandborn WJ, Rutgeerts PJ, Reinisch W *et al.* 751f one year data from the sonic study: a randomized, double-blind trial comparing infliximab and infliximab plus azathioprine to azathioprine in patients with Crohn's disease naive to immunomodulators and biologic therapy. Gastroenterology 2009;136:A-116.
78. van der Bijl AE, Breedveld FC, Antoni CE *et al.* An open-label pilot study of the effectiveness of adalimumab in patients with rheumatoid arthritis and previous infliximab treatment: relationship to reasons for failure and anti-infliximab antibody status. Clin Rheumatol 2008;27:1021–8.
79. Seiderer J, Brand S, Dambacher J *et al.* Adalimumab in patients with Crohn's disease—safety and efficacy in an open-label single centre study. Aliment Pharmacol Ther 2007;25:787–96.
80. Ho GT, Smith L, Aitken S *et al.* The use of adalimumab in the management of refractory Crohn's disease. Aliment Pharmacol Ther 2008;27:308–15.
81. Danese S, Mocciaro F, Guidi L *et al.* Successful induction of clinical response and remission with certolizumab pegol in Crohn's disease patients refractory or intolerant to infliximab: a real-life multicenter experience of compassionate use. Inflamm Bowel Dis 2008;14:1168–70.
82. Rubbert-Roth A, Finckh A. Treatment options in patients with rheumatoid arthritis failing initial TNF inhibitor therapy: a critical review. Arthritis Res Ther 2009;11 (Suppl 1): S1.
83. Targan SR, Feagan BG, Fedorak RN *et al.* Natalizumab for the treatment of active Crohn's disease: results of the ENCORE Trial. Gastroenterology 2007;132:1672–83.
84. Afif W, Loftus EV Jr, Faubion WA *et al.* Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. Am J Gastroenterol 2010;105:1133–9.
85. Kaplan GG, Hur C, Korzenik J *et al.* Infliximab dose escalation vs. initiation of adalimumab for loss of response in Crohn's disease: a cost-effectiveness analysis. Aliment Pharmacol Ther 2007;26:1509–20.
86. Sandborn WJ, Hanauer SB, Rutgeerts PJ *et al.* Re-induction and maintenance therapy with subcutaneous certolizumab pegol in patients with Crohn's disease following treatment failure: PRECiSE 4 results. Gastroenterology 2007;132:A505.
87. Fiorino G, Allez M, Malesci A *et al.* Review article: anti TNF-alpha induced psoriasis in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2009;29:921–7.
88. Haraoui B, Krelenbaum M. Emergence of Crohn's disease during treatment with the anti-tumor necrosis factor agent etanercept for ankylosing spondylitis: possible mechanisms of action. Semin Arthritis Rheum 2009;39:176–81.
89. Cohen SB, Emery P, Greenwald MW *et al.* Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 2006;54:2793–806.
90. Genovese MC, Becker JC, Schiff M *et al.* Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med 2005;353:1114–23.
91. Finckh A, Ciurea A, Brulhart L *et al.* B cell depletion may be more effective than switching to an alternative anti-tumor necrosis factor agent in rheumatoid arthritis patients with inadequate response to anti-tumor necrosis factor agents. Arthritis Rheum 2007;56:1417–23.
92. Finckh A, Ciurea A, Brulhart L *et al.* Which subgroup of rheumatoid arthritis patients benefits from switching to rituximab versus alternative anti-TNF agents after previous failure to anti-TNF agent? Ann Rheum Dis 2010;69:387–93.
93. Sandborn WJ, Hanauer S, Loftus EV Jr *et al.* An open-label study of the human anti-TNF monoclonal antibody adalimumab in subjects with prior loss of response or intolerance to infliximab for Crohn's disease. Am J Gastroenterol 2004;99:1984–9.
94. Vermeire S, Abreu MT, D'Haens G *et al.* Efficacy and safety of certolizumab pegol in patients with active Crohn's disease who previously lost response or were intolerant to infliximab: open-label induction preliminary results of the WELCOME study. Gastroenterology 2008;134:A-67–8.
95. Panaccione R, Sandborn WJ, D'Haens G *et al.* 920 Adalimumab maintains long-term remission in moderately to severely active Crohn's disease after infliximab failure: 1-year follow-up of gain trial. Gastroenterology 2008;134:A-133–4.
96. Oussalah A, Babouri A, Chevaux JB *et al.* Adalimumab for Crohn's disease with intolerance or lost response to infliximab: a 3-year single-centre experience. Aliment Pharmacol Ther 2009;29:416–23.
97. Lichtiger S, Present DH, Wu E *et al.* T1061 Improvement in short inflammatory bowel disease questionnaire scores in adalimumab-treated Crohn's disease patients who failed infliximab (CHOICE trial). Gastroenterology 2008;134:A-474–5.
98. Allez M, Vermeire S, Mozziconacci N *et al.* The efficacy and safety of a third anti-TNF monoclonal antibody in Crohn's disease after failure of two other anti-TNF antibodies. Aliment Pharmacol Ther 2010;31:92–101.
99. Lashner B, Colombel JF, Enns R *et al.* Natalizumab induces sustained response and remission in the absence of concomitant immunosuppressants in patients with crohn's disease who failed prior anti-TNFα therapy. Am J Gastroenterol 2007;102 (Suppl 2): S493.
100. Reinisch W, Sandborn WJ, Hommes DW *et al.* Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut 2011.
101. Teisner AS, Ainsworth MA, Brynskov J. Long-term effects and colectomy rates in ulcerative colitis patients treated with infliximab: a Danish single center experience. Scand J Gastroenterol 2010;45:1457–63.