ABSTRACT

Tumor necrosis factor (TNF) antagonists have substantially improved clinical response and remission rates in patients with Crohn’s disease and ulcerative colitis who have not responded adequately to conventional therapies. However, these protein-derived biologic agents are associated with varying degrees of immunogenicity, infusion and injection-site reactions, and loss of treatment response. Clearly, strategies are needed to predict, measure, and maintain response and prevent or restore lost treatment response. This article reviews initial response to treatment with monoclonal antibody-based TNF antagonists, discusses the possible mechanisms for loss of response, and describes strategies to minimize immunogenicity and prevent or restore lost treatment response. The article also addresses the significance of C-reactive protein in the variability of response to therapy, the role of serologic markers and various clinical factors in assessing and monitoring response, and the potential of pharmacogenomics to predict response and enhance drug efficacy and safety.

**Response to Anti-TNF Therapy**

**Initial Response Rates**

Before addressing specific strategies and exploring the role of pharmacogenomics, it is worthwhile to review initial response rates to infliximab, which is approved for the treatment of CD and UC, and other TNF antagonists, such as adalimumab and certolizumab pegol, that are being evaluated in phase III trials in patients with CD.

Studies evaluating infliximab have shown that it is highly effective in the treatment of luminal and fistulizing CD. In a 4-week, multicenter, double-blind, placebo-controlled, proof-of-concept study in patients with moderate to severe luminal disease that was resistant to conventional therapies, 54 of 83 patients receiving a single infusion of infliximab 5 mg/kg, 10 mg/kg, or 20 mg/kg had a clinical response within 4 weeks versus 4 of 24 patients receiving placebo.4 Clinical response was defined as a reduction of at least 70 points in the Crohn’s Disease Activity Index (CDAI) score. Response rates at 4 weeks were 41% in those receiving infliximab versus 12% in those receiving placebo. In addition, 33% of the patients receiving infliximab went into remission (defined as a CDAI score <150) versus 4% of patients receiving placebo.

However, the need for retreatment in patients with luminal CD subsequent to their response to the initial infusion was demonstrated in a study by Rutgeerts et al in which retreatment was shown to maintain response compared to patients who were subsequently randomized to placebo.1

A subsequent randomized, multicenter, double-blind, placebo-controlled study in 94 patients with draining abdominal or perianal fistulas of at least 3 months' duration demonstrated that intravenous (IV) infliximab 5 mg/kg or 10 mg/kg administered at weeks 0, 2, and 6 was significantly more effective than placebo in reducing the number of draining fistulas by at least 50% from baseline at 2 or more consecutive study visits (primary endpoint) and in promoting closure of all fistulas (secondary endpoint).6 Of the 31 patients randomized to 5 mg/kg and 32 patients randomized to 10 mg/kg, 68% and 55%, respectively, achieved the primary endpoint versus 26% of the 31 patients randomized to placebo. Rates for achieving the secondary endpoint were 55% in the 5 mg/kg group, 38% in the 10 mg/kg group, and 13% in the placebo group, with fistulas remaining closed for a median of 3 months.

In addition, many patients in the study responded before the second or third infusion, suggesting that 3 infusions were not necessary to reduce the number of draining fistulas and promote fistula closure.1,6 However, the mean duration of response of approximately 12 weeks after all 3 infusions demonstrated that infliximab did not “reset the immunostat” and that retreatment would be necessary to maintain response and remission.1

These studies led to 2 randomized trials of maintenance therapy—A Crohn’s Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen (ACCENT)—with ACCENT I involving 573 patients with luminal disease and a CDAI score of at least 220, and ACCENT II involving 306 patients with CD and at least 1 draining abdominal or perianal fistula of at least 3 months' duration.7,8

In ACCENT I, all patients received an IV infusion of infliximab 5 mg/kg at week 0 and were assessed for response at week 2. Those responding to the initial dose with a decrease in the CDAI of 70 points from baseline (58%) were randomized to repeat infusions of placebo at weeks 2 and 6 and every 8 weeks thereafter for 54 weeks (group I, n = 110); repeat infusions of infliximab 5 mg/kg at the same time points (group II, n = 113); or infliximab 5 mg/kg at weeks 2 and 6 followed by 10 mg/kg every 8 weeks (group III, n = 112). The prespecified co-primary endpoints of the trial were the proportion of patients who responded at week 2 and were in remission (CDAI <150) at week 30, and the time to loss of response.7 (Mechanisms accounting for loss of response and strategies to prevent or restore lost response are discussed in greater detail in the “Loss of Response” section of this article.)

At week 30, significantly more patients in groups II (39%) and III (45%) were in remission compared with group I (21%). Median time to loss of response was 38 weeks in group II and more than 54 weeks in group III compared to 19 weeks in group I. In addition, patients in groups II and III were more likely to maintain response and remissions while discontinuing corticosteroid therapy.7

In ACCENT II, patients with refractory fistulizing CD received a series of 3 infusions of infliximab 5 mg/kg at weeks 0, 2, and 6. A total of 282 patients—195 who responded at weeks 10 and 14 and 87 who had no response—were then randomized to infliximab 5 mg/kg every 8 weeks or placebo and followed for 54 weeks. The primary endpoint was time to loss of
response (reduction of 50% in the number of draining fistulas) among patients who responded at week 14 and underwent randomization.8

At week 54, 36% of patients receiving infliximab had no draining fistulas compared to 19% of patients receiving placebo. Time to loss of response was significantly longer in the patients receiving infliximab than in those receiving placebo (>40 weeks vs 14 weeks; \(P < .001\)).8

All of the infliximab trials described above demonstrated that maintenance therapy is necessary in most patients with CD and that regularly scheduled therapy is more beneficial than episodic “as needed” treatment. The latter was confirmed in another analysis of the ACCENT I study that directly compared scheduled and episodic treatment strategies.7 The study found that scheduled treatment resulted in better CDAI responses, higher response and remission rates, higher rates of mucosal healing, fewer hospitalizations, and less immunogenicity with no increase in adverse side effects.

Studies of other TNF antagonists have shown that they too are effective in inducing response and remission in patients with CD. In a multicenter, randomized, placebo-controlled, dose-ranging study evaluating adalimumab in 299 patients with moderately to severely active CD and no prior exposure to TNF antagonists, 30% of patients receiving the 2 higher (of 3) doses of the drug at weeks 0 and 2 achieved clinical remission at 4 weeks versus 12% of patients receiving placebo.9 Results were not dependent on baseline concentrations of C-reactive protein (CRP).

In this study, subcutaneous (SC) doses of adalimumab were 160 mg at baseline and 80 mg at week 2 (160 mg/80 mg), 80 mg/40 mg, and 40 mg/20 mg. Clinical remission was defined as a CDAI score of lower than 150, and clinical response was defined as a reduction in CDAI score from baseline of 70 or more or 100 or more points. Response rates among patients receiving the 160 mg/80 mg and 80 mg/40 mg doses were 56.5% for a reduction of 70 or more points (vs 35% in the placebo group) and 43% for a reduction of 100 or more points (vs 23% in the placebo group).9

A randomized, placebo-controlled trial evaluating 3 different doses of the TNF antagonist certolizumab pegol (CDP870) in 292 patients with moderate to severe CD found that clinical response and remission rates at 12 weeks were significantly higher in patients with elevated CRP levels who received the highest dose (400 mg SC at weeks 0, 4, and 8) than in those receiving placebo (53% vs 18%; \(P = .005\)).11 Rates for all doses in the group as a whole were higher than those seen with placebo, but the differences were not statistically significant. However, preliminary results from a 26-week, phase III trial have shown that certolizumab pegol was effective in inducing and maintaining response and remission in patients with moderate to severe CD regardless of CRP levels.12

**Attenuated Response**

Despite good initial response rates to anti-TNF agents, some patients with CD lose their response or have an attenuated response to therapy, and at least 33% who receive this therapy fail to show any useful response.13 However, studies have shown that patients with attenuated or lost response to infliximab may respond to treatment with other antibody-derived TNF agents.

In a study of 15 patients with active CD who had an attenuated response to infliximab, 7 patients had a complete response to adalimumab over a 6-month period, 4 had a partial response, 2 had no response, and 2 had inadequate follow-up.14 In another uncontrolled pilot study of adalimumab in 24 patients with CD who had a good initial response to infliximab but lost response over time or experienced acute or delayed infusion reactions, the investigators found that adalimumab produced a complete response in 5 patients and a partial response that was enhanced by dose escalation during maintenance therapy in 19 patients.15 All 24 patients were able to tolerate adalimumab. When these results are considered with similar findings from another pilot study evaluating the TNF antagonist CDP571 in 20 patients who had acute or delayed infusion reactions to infliximab,16 it is reasonable to conclude that patients who experience acute or delayed infusion reactions to infliximab can be safely retreated with other anti-TNF agents.17 Similar results regarding retreatment with other anti-TNF agents have been reported in patients with rheumatoid arthritis who experienced infusion reactions to infliximab.18

Efficacy data from another open-label pilot study evaluating adalimumab in patients with prior loss of response to infliximab have shown that 59% had a clinical response (ie, a reduction in CDAI score of 100 points) at 12 weeks, 29% were in clinical remission (CDAI <150), and 56% with draining fistulas at baseline had reduced the number of draining fistulas by at least 50%.19
LOSS OF RESPONSE

As noted earlier in this article, some patients lose responsiveness to infliximab over time or become intolerant to the drug. The major reasons for loss of response are: the development of antibodies to the drug, which increases the risk of infusion reactions; differences in acquired resistance to anti-TNF agents; and the development of noninflammatory signs and symptoms, such as bowel strictures, short bowel, or irritable bowel syndrome.20,21

IMMUNOGENICITY

All biologic agents, whether chimeric, humanized, or fully human, have the potential to be antigenic (ie, the ability of a molecule to be recognized by a pre-existing B- or T-cell receptor), immunogenic (development of an immune response), or tolerogenic (development of tolerance), depending on mode of administration, uptake by and costimulation of antigen-processing cells, and exogenous factors such as concomitant immune-suppressing therapies. Interpretation of immunogenicity may be complicated by different assay formats with differing sensitivities and cut-offs, different biologic epitopes, and interference of assay systems in the presence of the antigenic protein. Factors that increase immunogenicity include IV administration, low-dose exposure, and episodic administration. Immunogenicity can be reduced by SC administration, high-dose induction therapy, scheduled maintenance treatment, and administration with concomitant immune suppression. Ultimately, immunogenicity can be determined by the measurement of antibiologic antibodies, by measurement of concentrations of biologics, or by measurement of concentrations of TNF-α.22

Although all of the anti-TNF biologic agents have the potential to induce immunogenicity, there are more data on immunogenicity to infliximab because the drug has been available for the past 8 years. Several studies have shown that infliximab is immunogenic, leading to the formation of human antichimeric antibodies, also known as antibodies to infliximab (ATI), in patients with CD, rheumatoid arthritis, and ankylosing spondylitis.4-8,20,21,23,24 Some of these studies and others have investigated the incidence and pharmacokinetics of ATI, the impact of ATI on long-term efficacy and relationship to adverse effects, and strategies to reduce ATI formation.7,4,20,21,23-27 Data regarding immunogenicity to adalimumab and certolizumab pegol have been less forthcoming.28 In rheumatology trials, antibodies to adalimumab appear in approximately 6% of patients and are reduced by coadministration of methotrexate.29

Infliximab immunogenicity

The lower incidence of ATI in patients receiving concomitant immunomodulatory therapy was clearly demonstrated in ACCENT I, ACCENT II, and a study by Baert et al.7,8,20 In ACCENT I, the overall incidence of ATI was 28% in patients receiving episodic treatment (ie, group I, which received a single infliximab dose at week 0 and placebo infusions at weeks 2 and 6 and every 8 weeks thereafter), 9.1% in group II, and 6.3% in group III.30 However, the incidence of ATI was lower in patients in all 3 groups who received concomitant therapy with immunomodulators (Figure 1).21 In ACCENT II, the incidence of ATI was 24% in patients who received no concomitant medications at baseline, 13% in patients who received steroids, 11% in those who received immunomodulators, and 3.7% in those who received both.30 In a study conducted by Baert et al in 125 consecutive patients with CD who received 1 to 17 (mean, 3.9) infliximab infusions episodically over 10 months, the overall incidence of ATI was 61%.20 When immunomodulator was considered, a significantly lower proportion of patients receiving these drugs were ATI positive compared to patients who were not receiving them (43% vs 75%; P <.01).

Figure 1. Incidence of ATI with and without Immunomodulators in ACCENT I

ACCENT = A Crohn’s Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen; ATI = antibodies to infliximab.
Clinical impact of ATI

The study of Baert et al also evaluated concentrations of infliximab and ATI, in addition to the impact of ATI on infusion reactions and loss of response.20 As shown in Figure 2, ATI reduce serum infliximab levels, increase the risk of infusion reactions, and reduce the duration of response to treatment. ATI concentrations 80 µg/mL or more before an infusion predicted a significantly shorter duration of response—35 days versus 71 days among patients with concentrations 80 µg/mL or less (P<.001)—and a 24-fold increased risk of infusion reactions (P<.001). Infliximab concentrations were also significantly lower at 4 weeks among patients who had an infusion reaction than among those who did not (P<.001).

In addition, infusion reactions were associated with significantly shorter duration of clinical response. The median duration of clinical response in patients who had infusion reactions was 38.5 days versus 65 days among those who did not have an infusion reaction (P<.001).20

In another study investigating the impact of ATI on clinical response, Farrell et al found that 68% of 53 patients treated with 199 infusions of infliximab 5 mg/kg responded to initial therapy, but that 42% of them lost response.27 Of the 15 patients who lost their initial response, 11 were positive for ATI, including all 7 who also had serious infusion reactions. ATI developed in 36% of the group as a whole. However, 86% of patients who did not have ATI responded to retreatment versus 48% of those who were ATI positive. Patients were retreated with a second infliximab infusion within 8 weeks of the first infusion or concurrent immunosuppressants; both strategies significantly reduced ATI formation.

The study investigators subsequently evaluated the effects of IV hydrocortisone premedication versus placebo on ATI levels in 80 patients.27 They found that pretreatment with IV hydrocortisone significantly reduced ATI levels compared to placebo, but that it did not eliminate ATI formation or infusion reactions.

Minimizing the impact of ATI

Data from trials evaluating infliximab in CD have suggested several strategies to minimize the clinical impact of ATI (Figure 3). However, additional strategies need to be considered when there is loss of response to therapy. First, it is worth noting that loss of response is not always due to ATI. It may result from noninflammatory signs and symptoms, such as bowel strictures or from acquired resistance to anti-TNF agents.21 Therefore, it is crucial to reassess patients for inflammatory signs and symptoms, with laboratory tests for CRP levels, colonoscopy, and radiologic procedures, to confirm that active disease is present. If reassessment confirms that active inflammation is present, then ATI need to be evaluated further, as summarized in Figure 4.

Several studies have shown that using other TNF antagonists, such as adalimumab and certolizumab pegol, is a viable alternative in patients with CD with prior loss of response to infliximab.11,12,15,19 These agents appear to be less immunogenic than infliximab,31 and results thus far have been promising.

However, as is the case in patients with rheumatoid arthritis, patients with CD often respond to alternative anti-TNF antibodies or antibody fragments after loss of response to an initial biologic agent, but the results are not quite as good with the second agent. The best overall approach at present is to use the dose optimization strategies outlined in Figure 3 rather than “immunize” patients to infliximab with the most immunogenic regimen (ie, a single dose of the drug without immunomodulating therapy, followed by “episodic” or “as needed” dosing).31 These strategies are based on the best available evidence from observational studies.31
Another approach to preventing immunization is to utilize concomitant immune suppression with methotrexate, a thiopurine antimetabolite, or pretreatment with high-dose corticosteroids.28,32,33

**ROLE OF PHARMACOGENOMICS**

Pharmacogenomics is an extension of pharmacogenetics, a science rooted in a number of clinical observations that predicted genetic alterations of drug response. Additional case discoveries and systematic case studies led to the recognition of systematic pharmacogenetic differences between human populations and the realization that most drug-response differences in humans were multifactorial, resulting from numerous genetic alterations plus environmental factors.3 Recognition of these complexities, along with the advance of genetics into genomics, led to the broader science of pharmacogenomics, which studies the genetic polymorphisms that underlie the variability in drug response between individuals and the relationship between drug effects and the genome.34,35 As such, pharmacogenomics has the potential to create “personalized medicine” (ie, making drugs safer and more effective through their action on genetic variants so that the drugs fit the individual’s genes) and to develop DNA-based tests to maximize drug efficacy and enhance drug safety.3,36

Two branches of pharmacogenomics have emerged: structural pharmacogenomics, which maps the DNA sequence of whole genomes (genotypes), including genetic variations; and functional pharmacogenomics, which can simultaneously assess the levels of expression of thousands of genes.35 Together, both branches have generated massive databases that may substantially improve the drug development process with regard to identifying drug targets, evaluating toxicity, classifying diseases, evaluating drug formulations, assessing drug responses and treatment, and developing personalized medicines. However, much more clinical and translational research is needed, particularly in the latter area.

At present, personalized medicine is best represented by a physician’s attention to patient population factors that indicate less genetic variation than is typical of the general population (ie, a patient’s age, gender, race, and ethnicity).37 However, there has been some progress in using genomic techniques to predict which patients with CD will respond to anti-TNF or immunomodulator therapy and which patients will not.13,38-41

In a review article, Shetty and Forbes noted that the need to predict response to anti-TNF therapy and anticipated relapse was extremely important because at least 33% of patients with CD who are candidates for therapy with TNF antagonists fail to show any useful response.13 With the need to identify predictive factors in mind, the investigators noted several TNF polymorphisms in CD and UC that were possibly associated with poor response to infliximab, including increasing mucosal levels of activated nuclear factor kappa B, a pro-inflammatory transcription factor; homozygosity for the polymorphism in exon 6 of TNF receptor 2 (genotype Arg196Arg); positivity for pANCA; and the presence of increased numbers of activated mononuclear cells in the lamina propria producing interferon-γ and TNF-α.

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**Figure 3. Strategies to Minimize ATI Impact**

- 3-dose induction regimen (infliximab 5 mg/kg) to maximize efficacy/tolerance
- Scheduled maintenance regimen (every 8 weeks) to increase duration of response
- Concurrent immunomodulators to reduce ATI
- Pretreatment with high-dose corticosteroids

**Figure 4. Assessing Loss of Response**

- Antibodies to infliximab
  - (+) (-, no infliximab) (-, infliximab present)
  - ↓
  - Alternative anti-TNF agent
  - Reduce infusion interval or increase dose to 10 mg/kg
  - Alternative target

ATI = antibodies to infliximab.

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**Table 1. Strategies to Minimize ATI Impact**

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<th>Strategy</th>
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**Table 2. Assessing Loss of Response**

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Alternative |

- Reduce infusion interval or increase dose to 10 mg/kg

**TNF** = tumor necrosis factor.
In contrast, the authors of another review article noted that polymorphisms in TNF receptor 1 and TNF receptor 2 were not associated with treatment response. They also found no association between treatment response and the 3 mutations in the CARD15 gene that are independently associated with susceptibility to CD.

Characterizing the development of anti-TNF agents as a simple and logical molecular strategy with complex clinical consequences, Waetzig and Schreiber reviewed the mechanisms by which infliximab inhibits the production of TNF-α. However, in their discussion of the variability of response among patients treated with the drug, they concluded that response to TNF antagonists was not determined by polymorphisms in the TNF, TNF receptor, or NOD2 genes, but may be determined by variations in other genes in or outside the TNF signaling cascade.

In a review article describing the genetic variants that influence the efficacy or toxicity of infliximab and other drugs commonly used to treat IBD, Pierik et al noted that there was no difference in treatment response, as measured by CDAI, in patients with CD receiving infliximab who were genotyped for R702W, G908R, and 1007InsC in CARD15. There were also no significant associations between treatment response and single nucleotide polymorphisms (SNPs) in the main target molecule of TNF-α (-238, -308, -376, -857, -1031) and its receptors (-609 and +36 or P12P in TNF receptor 1 and 168 or L56L, 587 M196A, 1663, and 1690 in TNF receptor 2).

However, because the efficacy of infliximab in CD is partially due to the drug’s ability to induce apoptosis of activated T lymphocytes, it was thought that investigations of the effect of polymorphisms in apoptosis genes in patients with luminal or fistulizing CD would yield valuable data with regard to predicting response to infliximab therapy. One such study, involving a cohort of 287 patients treated with infliximab for luminal or fistulizing CD, found that 74.7% of patients carrying the Fas ligand -843 CC/CT genotypes responded to therapy compared to 38.1% of those with the TT genotype. In the same cohort, all patients with the caspase 9 93 TT genotype responded to therapy compared to 66.7% of patients with the CC and CT genotypes.

A separate study investigating the association between the FCGR3A-158 polymorphism (expressed in macrophages and natural killer cells) and response to infliximab in 142 patients with refractory luminal CD and 58 patients with fistulizing CD found that 82.9% of those with the VV genotype and 72.7% of those with VF or FF genotypes had a clinical response to the drug, as measured by CDAI. In addition, all patients with the VV genotype had a biological response to infliximab, defined as a decrease in CRP of at least 25% from baseline, versus 69.8% of patients with 1 or more F alleles. These findings suggest that patients with CD with the FCGR3A-158 VV genotype have a better biological response, and possibly a better clinical response, to infliximab.

In another review article, Egan et al pointed out that clinically significant genetic variations consist of SNPs within genes that affect drug disposition and drug targets. Although relatively few clinically important examples of inherited traits that affect drug responses have been studied in detail thus far, the pharmacogenetics of thiopurine methyltransferase have been studied and are highly relevant to the response to azathioprine/6-mercaptopurine in patients with CD or UC. Those patients with 2 normal alleles of the gene encoding thiopurine methyltransferase metabolize and clear thiopurines such as azathioprine/6-mercaptopurine rapidly, whereas those with 2 variant alleles of the gene clear them very slowly, and those with 1 normal and 1 variant allele are intermediate. Slow and intermediate metabolizers are predisposed to high active thiopurine levels and are at higher risk for developing bone marrow suppression.

The authors also noted that the use of high-throughput SNP genotyping and careful phenotypic characterization of CD and UC enhanced the potential of pharmacogenomics to identify individual biomarkers that predict the relative likelihood of benefit or risk from a therapeutic intervention.

**Strategies to Monitor Patients for Immunogenicity and Other Toxicities**

Because therapeutic proteins, such as infliximab, are associated with the formation of antibodies, which increase the risk of serious adverse reactions and infections and lead to loss of response, it is essential to assess patients for continued response and monitor patients for the development of antibodies and adverse events during induction and primarily
during maintenance therapy. One gauge that can be used to assess and monitor anti-TNF therapy is the need for dose escalation of the TNF antagonist and intensification of cotherapy over time.

A study of nearly 1200 patients with rheumatoid arthritis (representing 1450 patient-years of anti-TNF treatment) found that those treated with infliximab were more likely to have a reduced therapeutic response after the first 6 months of treatment and were more likely to require intensification of cotherapy with disease-modifying antirheumatic drugs than patients receiving etanercept or adalimumab. The study investigators noted that the reduced therapeutic response to infliximab over 6 months was suggestive of acquired drug resistance. Although the study involved patients with rheumatoid arthritis, the findings are also applicable to the assessment of response in patients with CD.

In addition, a general proviso should be that clinicians remain vigilant with regard to the occurrence of serious events, such as serum sickness-like reaction, opportunistic infections and sepsis, and autoimmune disorders. Reports associating anti-TNF therapy with an increased risk of opportunistic infections, particularly tuberculosis and other intracellular pathogens, have raised concerns and prompted the US Food and Drug Administration to recommend tuberculin skin testing in all candidates for infliximab therapy. However, a study of 70 patients with CD and 12 patients with other inflammatory bowel conditions found that none of them had a positive response to skin tests administered before or between infliximab infusions. Moreover, a significantly higher proportion of patients who also received corticosteroids and/or immunomodulators for at least 1 month were anergic compared to those who did not receive these drugs (83% vs 43%; \( P < .002 \)).

Given the high prevalence of anergy, the study investigators concluded that a negative tuberculin skin test alone was an unreliable indicator of exposure to tuberculosis. They recommended a more thorough evaluation of tuberculosis risk in patients being considered for infliximab therapy, including a skin test, a detailed history of travel, other exposure to tuberculosis, and symptoms such as chronic cough and weight loss, and a chest X-ray. In addition, the use of the QuantiFERON (Cellestis Limited, Carnegie, Victoria, Australia) assay may identify patients at risk for reactivation of tuberculosis in the setting of anergy or previous immunization with bacillus Calmette-Guérin.

CONCLUSIONS

Studies have shown that infliximab, thus far the only TNF antagonist approved for the treatment of CD, is highly effective in treating the luminal and fistulizing forms of the disease. However, other investigations have shown that many patients treated with TNF antagonists lose their response over time and that at least 33% fail to show any clinically meaningful response.

Immunogenicity (ie, the formation of antibodies to TNF antagonists) is the major reason for loss of response and adverse infusion reactions, although differences in acquired drug resistance to these agents and the development of noninflammatory signs and symptoms, such as bowel strictures, also play a role.

Strategies to minimize the impact of antibody formation, particularly to infliximab, include a 3-dose induction regimen, a scheduled maintenance regimen, the concurrent use of immunomodulators, and pretreatment with high-dose corticosteroids. The use of other TNF antagonists, such as adalimumab and certolizumab pegol, which appear to be less immunogenic than infliximab and have been shown to be effective in patients with prior loss of response to infliximab, is another alternative. Both of these agents are currently being evaluated in phase III trials involving patients with CD.

Although all TNF antagonists target TNF, there is considerable variability in response to these agents among patients. The science of pharmacogenomics, which studies the genetic polymorphisms that underlie the variability in drug response between individuals, has the potential to make drugs safer and more effective through their action on genetic variants so that the drugs fit the individual’s genes.

It is essential to assess and monitor patients for the development of antibodies and adverse events during induction and maintenance therapy. Clinicians should consider patient factors that indicate reduced genetic variations (ie, age, gender, and race) in assessing and predicting patient response to therapy, and they should remain vigilant with regard to the development of antibodies and the occurrence of serious adverse events.
REFERENCES


