Optimizing Anti-TNF Treatment in Inflammatory Bowel Disease

PAUL RUTGEERTS, GERT VAN ASSCHE, and SÉVERINE VERMEIRE
Department of Medicine, Division of Gastroenterology, University of Leuven, 3000 Leuven, Belgium

Infliximab, the chimeric monoclonal immunoglobulin (Ig)G1 antibody to tumor necrosis factor (TNF) has changed our therapy of Crohn's disease. Infliximab is indicated in refractory luminal and fistulizing Crohn's disease. In patients with luminal disease, a single intravenous (IV) dose of 5 mg/kg is efficacious; in fistulizing disease, an IV loading therapy of 5 mg/kg at weeks 0, 2, and 6 is advocated. Because the majority of patients will relapse if not re-treated, a long-term strategy is necessary. The optimal long-term approach is systematic retreatment with 5 mg/kg every 8 weeks. Episodic therapy on relapse also is possible but is less efficacious and frequently is associated with problems resulting from the formation of antibodies to infliximab (ATI). If treatment is episodic, maintenance therapy with immunosuppression (azathioprine [AZA]/6-mercaptopurine [6-MP] or methotrexate) is mandatory. Trial data suggest that systematic maintenance with 8 weekly doses of infliximab decreases the rate of complications, hospitalizations, and surgeries. These effects probably are achieved thanks to thorough healing of the bowel. Infliximab also is indicated in treating corticosteroid-dependent Crohn's disease and extraintestinal manifestations of Crohn's disease. There are no data yet that support its use as first-line therapy. The data in ulcerative colitis (UC) are conflicting and we should await the results of 2 large controlled trials (ACT1 and ACT2) to position infliximab in the treatment of UC. Other anti-TNF strategies have been less effective than infliximab in the treatment of IBD until now. The results with thalidomide are promising but much more research into small molecules inhibiting TNF and other proinflammatory cytokines is necessary. Safety problems with antibody treatment mainly concern immunogenicity leading to infusion reactions, loss of response, and serum sickness–like delayed infusion reactions. The rate of opportunistic infections is increased mainly in patients treated concomitantly with immunosuppression. Other adverse events associated with anti-TNF strategies are demyelinating disease and worsening of congestive heart failure. Malignancy rates in patients treated with anti-TNF strategies do not seem to be increased.

The advent of infliximab (Remicade; Centocor, Malvern, PA) has greatly improved our treatment of Crohn's disease. Crohn's disease is a disabling bowel disorder occurring mostly in young patients in early adulthood, in the most productive period of their lives. Patients with Crohn's disease experience a greatly decreased quality of life. Up to 70% of patients with Crohn's disease undergo surgery and 30% undergo repeated resections. The disease also causes a great psychologic burden.

Our therapies frequently were deficient for induction of remission as well as for maintenance of disease control until the late 1990s when the first biological was introduced in the clinic.

Glucocorticosteroids induce remission in 48% of patients and improve symptoms in another 32% within 30 days of treatment start, whereas 20% of the patients are resistant from onset.[1] At 1 year, however, 45% of the patients who experienced initial improvement became glucocorticosteroid dependent. Faubion et al.[2] confirmed the limited efficacy of glucocorticosteroids for the treatment of Crohn's disease and described similar results for ulcerative colitis (UC). Relapse after weaning from glucocorticosteroids in responders with Crohn's disease occurs early and continued therapy with glucocorticosteroids for 1 year after control of disease does not maintain remission.[3] Moreover, side effects of glucocorticosteroids are important.

Before the era of biologicals and the widespread use of immunosuppressive agents only 42% of patients with Crohn's disease overall were relapse free at 2 years after initial diagnosis, and 12% were relapse free after 10 years. Ten percent of the patients had continuously active disease at 2 years and 1% had continuously active disease at 10 years.[4]

In patients with colorectal Crohn's disease,[5] the cumulative risk for major surgery at 10 years after diagnosis amounted to 49% and the risk for a permanent stoma was 25%. When Lapidus et al.[5] compared the cumulative

Abbreviations used in this paper: ATI, antibodies to infliximab; AZA, azathioprine; CRP, C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; IL, interleukin; RA, rheumatoid arthritis; 6-MP, 6-mercaptopurine; TNF, tumor necrosis factor.

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frequencies of surgery for the periods of diagnosis between 1960–1974 and 1975–1989 they found no significant differences, clearly showing the lack of progress in medical treatment of Crohn's disease. Only patients responding to immunosuppression were well for long periods of time. However, these drugs act slowly[6] and the success rate of immunosuppression with azathioprine (AZA) or its metabolite 6-mercaptopurine (6-MP) for maintenance is not completely clear. In the study by Candy et al.,[7] 42% of patients treated with AZA were in remission at 15 months after induction with glucocorticosteroids as compared with only 7% in the placebo group. Patients controlled with AZA for at least 6 months had a chance of relapse of 11% at 1 year, 22% at 3 years, and 32% at 5 years.[8] Young women with long delay in achieving remission are especially at risk for relapse. Ten percent of the patients did not tolerate AZA/6-MP. Therefore, it seems that immunosuppression with AZA/6-MP benefits no more than half of the patients refractory to or dependent on glucocorticosteroids, with a 5% to 10% relapse rate.

Methotrexate 25 mg/wk intramuscularly induced remission at 12 weeks in 39% of patients with chronically active disease despite at least 3 months of glucocorticosteroids therapy and is an alternative for patients not responding to or intolerant of AZA/6-MP.[9] Methotrexate 15 mg/wk intramuscularly maintained this remission in 65% of the patients in comparison with 39% given placebo.[10]

Chronic perianal fistulae greatly impair the quality of life in patients with Crohn's disease. Response to antibiotics is mostly incomplete and transient. Less than half of the patients respond to immunosuppression. For fistula healing the mean time to response to 6-MP is 3.1 months, with a maximal response at 8 months. A complete response is observed in 31% of the patients.[6] Severe anal Crohn's disease in nonresponders often leads to stricture or incontinence caused by destruction of the sphincter apparatus, which may necessitate proctectomy, colostomy, or ileostomy.

For patients in whom Crohn's disease is not controlled adequately with conventional therapy, for patients in whom control of the disease is not maintained long term on immunosuppression, and for patients with progression of perianal Crohn's disease, infliximab is a very important therapy. There is also evidence that infliximab may alter the course of Crohn's disease long term. Moreover, the spectrum of indications is broadening and includes extraintestinal disease and potential indications are first-line therapy in Crohn's disease, UC, and refractory pouchitis.

Infliximab (Remicade, Centocor) is an intravenously administered chimeric monoclonal immunoglobulin (Ig) G1 antibody to tumor necrosis factor (TNF). It is composed of human constant and murine variable regions.

In the United States, Remicade is approved for reducing signs and symptoms and inducing and maintaining clinical remission in patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Remicade also is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in patients with fistulizing Crohn's disease.

The Food and Drug Administration recommends a dose of 5 mg/kg Remicade given as an induction regimen at 0, 2, and 6 weeks, followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of moderately to severely active Crohn's disease or fistulizing disease. For patients who respond and then lose their response, consideration may be given for treatment with 10 mg/kg. Patients who do not respond by week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue Remicade in these patients.

In Europe, Remicade is approved for (1) the treatment of severe active Crohn's disease in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and an immunosuppressant, or who are intolerant to or have medical contraindications for such therapies; and (2) the treatment of fistulizing Crohn's disease in patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage, and immunosuppressive therapy).

The Committee for Proprietary Medicinal Products recommendations for severe active Crohn's disease are as follows: 5 mg/kg given as an intravenous infusion over a 2-hour period. Available data do not support further infliximab treatment in patients not responding within 2 weeks to the initial infusion. In responding patients, the alternative strategies for continued treatment are as follows: (1) maintenance therapy of additional infusions of 5 mg/kg at 2 and 6 weeks after the initial dose, followed-up by infusions every 8 weeks or (2) readministration of an infusion of 5 mg/kg if signs and symptoms of the disease recurs.

For fistulizing Crohn's disease, an initial 5-mg/kg infusion given over a 2-hour period is to be followed-up with additional 5-mg/kg infusion doses at 2 and 6 weeks after the first infusion. If a patient does not respond after these 3 doses, no additional treatment with infliximab should be given. In responding patients, the strategies

for continued treatment are as follows: (1) additional infusions of 5 mg/kg every 8 weeks or (2) readministration if signs and symptoms recur followed-up by infusions of 5 mg/kg every 8 weeks.

Infliximab: Mechanisms of Action

TNF-α is a key proinflammatory cytokine in Crohn's disease and in other chronic inflammatory conditions including rheumatoid arthritis (RA) and psoriasis. TNF-α is first produced as a 26-kilodalton transmembrane protein with an intracellular tail that is cleaved by the metalloproteinase TNF-α converting enzyme and secreted as a 17-kilodalton soluble protein. This form aggregates to form trimers that interact with 2 receptors to exert its action: the p55 TNF receptor 1 and the p75 TNF receptor 2. TNF is produced mainly by activated macrophages and T lymphocytes, among other cells. TNF induces other proinflammatory cytokines including interleukin (IL)-1 and IL-6 and enhances leukocyte migration by inducing expression of adhesion molecules by endothelial cells and leukocytes. TNF activates leukocytes and induces acute-phase reactants and metalloproteinases. The number of TNF-producing cells is greatly increased in the lamina propria in the bowel of patients with Crohn's disease[11,12] and increased concentrations of TNF have been found in the stools of children with Crohn's disease.[13]

Infliximab binds specifically to human TNF-α with an association constant of 10^{10} mol/L^{-1}. Pharmacokinetics of infliximab after intravenous (IV) infusion is characterized by a half-life of 9.5 days.[14] A dose-dependent maximum serum concentration of infliximab is found and it amounts to 118 μg/mL at a dose of 5 mg/kg after intravenous infusion. Clearance of infliximab from the circulation is 9.8 mL/h. At week 12, infliximab levels are no longer detectable (median concentration <0.1 μg/mL) with the 5 mg/kg dose but with a dose of 10 mg/kg IV therapeutic concentration is maintained for a longer period. The exact level of infliximab needed to exert its therapeutic effect has not been determined up until now. A dose of 1 mg/kg is not effective in Crohn's disease and a dose of 3 mg/kg has not been tested.

In parallel with infliximab levels the serum levels of TNF paradoxically increase from low levels (5–25 pg/mL) before infliximab to levels as high 50 pg/mL at 72 hours. The TNF levels measured, however, are complexed with infliximab and are not bioreactive.

The effect of infliximab on the acute-phase inflammatory response in responders as assessed by C-reactive protein (CRP) and IL-6 levels is very rapid. CRP levels and IL-6 levels normalize at 2 weeks but start to increase again in a percentage of patients from week 8 on.

The mechanism of action of infliximab is not well understood. Neutralization of soluble TNF is achieved with different anti-TNF antibodies including the humanized IgG4 antibody CDP571 and the TNF-α neutralizing chimeric fusion protein, etanercept, consisting of the extracellular portion of the p75 TNF receptor linked to the Fc domains of a type 1 human Ig (IgG1). CDP571 is less effective than infliximab in Crohn's disease[15] and etanercept is not effective,[16] showing that mere neutralization of TNF is not the main therapeutic effect. Blockade of other proinflammatory signals or molecules that are up-regulated by TNF-α also play a role. After IV infliximab administration, a clear increase of lymphocyte and monocyte counts in the blood is observed accompanied by a decrease of neutrophils between 2 and 14 weeks after infusion, suggesting that this anti-TNF strategy down-regulates expression of adhesion molecules, resulting in decreased migration of these cells to the target organ. In this respect the effect of infliximab may be compared with that of the anti-α4 integrin antibody, natalizumab[17] (Antegren-Elan, Dublin, Ireland). A key effect of infliximab is the disappearance of inflammatory cells from the previously inflamed bowel mucosa. Immunohistochemical studies of the inflamed bowel mucosa before and 4 weeks after infliximab administration showed a significant reduction in the number of activated T cells in the lamina propria.[18] The percentage of cells with positive stainings for intercellular adhesion molecule-1 and lymphocyte function–associated antigen 1 were decreased as well as the numbers of Th1 cells and TNF-α–positive monocytes and macrophages.

This effect of infliximab is achieved by lysis of inflammatory cells carrying membrane-bound TNF-α. The main mechanism probably is induction of apoptosis. Lamina propria T cells from patients with Crohn's disease are resistant to apoptosis. Lugering et al.[19] showed that infliximab at therapeutic concentrations induced apoptosis of peripheral blood monocytes from healthy volunteers and patients with Crohn's disease in a dose-dependent manner by activation of caspase-8, -9, and -3 in a Fas-independent manner. Monocyte apoptosis could be shown in vivo as soon as 4 hours after treatment with infliximab. ten Hove et al.[20] showed that infliximab induced apoptosis of lamina propria T cells in vivo and in the CD3-/CD28-activated T-cell line (Jurkat cells). The group from Amsterdam expanded on these observations and showed that in contrast to etanercept, infliximab binds to activated peripheral blood and lamina propria

Table 1. Indications for Induction and Maintenance Infliximab in Patients With IBD

Definite	Potential	No
Refractory luminal (including upper gastrointestinal) Crohn's disease	First-line therapy UC	Fibrostenosis only
Steroid-dependent Crohn's disease	Indeterminate colitis	Refractory anemia
Refractory fistulizing Crohn's disease	Refractory pouchitis	
Systemic manifestations of IBD	Primary sclerosing cholangitis	
Ankylosing spondylitis and sacroiliitis		
Pyoderma gangrenosum		
Chronic uveitis		
Metastatic Crohn's disease		

cells and induced apoptosis via activation of caspase 3.[21] In contrast, Ringheam et al.[22] could not show apoptosis of monocytes by infliximab but pretreatment of monocytes with infliximab resulted in a decreased production of TNF and other proinflammatory cytokines on stimulation with bacterial products. There are data that infliximab also induces cell lysis through complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity.[23] The relative contribution of each of these mechanisms of cell death to the lasting effect of infliximab is not known.

Clinical Use of Infliximab in Crohn's Disease

The first patient with Crohn's disease treated with infliximab was reported by Derkx et al.[24] in 1993. Trials with this drug were then already ongoing in patients with RA.[25] The dramatic effect of infliximab in a child with extremely severe Crohn's disease led to an open study confirming the beneficial effects of infliximab, which was called cA2 at the time.[26] Because the development of this therapy has been very rapid, infliximab reached the U.S. market in 1998.

We discuss the present state of the use of infliximab in inflammatory bowel diseases. The indications for infliximab are summarized in Table 1 and contraindications are summarized in Table 2.

Infliximab for Refractory Luminal Crohn's Disease

An intravenous infusion of infliximab over 2 hours is efficacious therapy for refractory luminal Crohn's disease. In the study by Targan et al.,[27] 50%–81% responded to doses of 5, 10, or 20 mg/kg vs. 17% for placebo at 4 weeks and 33% of patients achieved remission vs. 4% for placebo. In the large (n = 573) ACCENT I trial,[28] 58% of patients responded by week 2 and 27% of patients were in remission. At week 10, 69% responded and 42% reached remission in the loading-dose group. Although this loading dose of 3 infusions of 5 mg/kg at 0, 2, and 6 weeks resulted in a significantly higher response rate at 10 weeks (65% vs. 52%, $P = 0.035$), a single infusion at baseline certainly can be used but most patients will need maintenance therapy with infliximab even if treated with concomitant immunosuppression. Without repeated therapy 37% of patients will suffer relapse of their disease by 12 weeks.[27]

Although the Targan et al.[27] and ACCENT I trials[28] have been criticized for the fact that not all patients included were truly refractory, this does not invalidate the results. Some patients indeed had only failed 5-aminosalicylic acid and many were not managed optimally with immunosuppression. In these studies the dose of concomitant immunosuppression was kept stable during the follow-up period. Subgroup analysis, based on clinical parameters including concomitant therapy, did not show significant differences between the groups as far as response to treatment was concerned. In open cohort studies, however, it was shown clearly that patients using immunosuppressives had a better short-term response to infliximab.[36–38]

In the maintenance phase after the Targan trial,[27] patients received 10 mg/kg infliximab every 8 weeks or placebo for 44 weeks with infusions at 0, 12, 20, 28, and 36 weeks. The interval for the prophylactic infusions of 8 weeks was chosen based on pharmacokinetics of infliximab. At 1 year, 62% of the patients had maintained response and 53% had maintained remission with repeated infliximab infusions of 10 mg/kg, whereas only 37% were still responding when receiving placebo with 20% still in remission ($P = 0.013$).

Table 2. Contraindications for Infliximab Therapy

Definite	Relative
Active abscess	Inefficacy
Suspected active tuberculosis	First infusion
Intestinal obstruction	Subsequent infusions
Multiple sclerosis or optical neuritis	Absence of inflammatory activity
Class III/IV congestive heart failure	
Previous lymphoma	
Uncontrolled infusion reaction	
ATI related	
IgE mediated	

Table 3. Efficacy of Maintenance With Every 8 Weeks Infliximab 5 mg/kg, 10 mg/kg After a Loading Dose Compared With a Single 5-mg/kg Dose Followed by Placebo Infusions: Analysis of Primary Endpoints

	Remission at 30 wk	Median time to relapse (wk–interquartile range)	Discontinued GCS and remission
Infliximab 5 mg/kg (n = 113)	39%	38 (15 to >54)	
Infliximab 10 mg/kg (n = 112)	45%	>54 (21 to >54)	
Infliximab combined (n = 225)	42%[a]	46 (17 to >54)[a]	29%[a]
Placebo (n = 110)	21%	19 (10–45)	5%

NOTE. Patients were censored when they failed treatment.
[a]Statistically significant at the 1% level.

In the ACCENT I long-term maintenance trial, 2 different analyses were performed. The placebo patients only received a 5 mg/kg infusion at week 0 and placebo at 2, 6, 14, 22, 30, 38, and 46 weeks. The 5-mg/kg group received 5 mg/kg at week 0 as well as at each of the other time points. The 10-mg/kg group received 5 mg/kg at weeks 0, 2, and 6, and 10 mg/kg at weeks 14, 22, 30, 38, and 46.

The first analysis[28] looked at the prespecified endpoints being the proportion of patients who responded at week 2 and who were in remission (Crohn's Disease Activity Index <150) at week 30 and the time to loss of response up to week 54. Loss of response was defined as a Crohn's Disease Activity Index of at least 175, with an increase of at least 35% and a Crohn's Disease Activity Index of at least 70 points more than the week 2 Crohn's Disease Activity Index score for at least 2 consecutive visits (≥21 days). The data are summarized in Table 3. Systematic maintenance with infliximab doubled the rate of patients in remission at 1 year (42% vs. 21%) as compared with only induction with 5 mg/kg.

The second analysis[40] looked at the outcome in all patients, including nonresponders at 2 weeks and allowing cross-over to higher doses (i.e., to episodic 5 mg/kg in the placebo group, episodic step-up to 10 mg/kg in the 5-mg/kg group, and 15 mg/kg in the 10-mg/kg group from 14 weeks on). Nearly half (49%) of the patients in the placebo group had to cross-over to episodic therapy with 5 mg/kg, compared with 30% in the every 8 weeks 5-mg/kg group and 26% in the every 8 weeks 10-mg/kg group. Among patients who lost response to 5 mg/kg or 10 mg/kg, approximately 80% to 90% re-established response by stepping up to 10 mg/kg and 15 mg/kg, respectively.

By using this flexible treatment regimen with the possibility for a step-up of dose the clinical remission and response rates in the combined (5 and 10 mg/kg) scheduled strategy groups (41% and 63%, respectively) were not significantly better than those in the episodic 5-mg/kg strategy group (35% and 56%, respectively).

A significantly greater proportion of patients on steroids at baseline (51% for all groups) and treated with systematic 5 mg/kg (44%) and 10 mg/kg (47%) of infliximab were able to stop glucocorticosteroids and remain free from this drug than the proportion of patients treated episodically (29%).

The quality of life in patients with luminal disease in the ACCENT I trial as measured by using the Inflammatory Bowel Disease Questionnaire (IBDQ) score was low at baseline, with a median of 126 for the episodic group, 126 for the 5-mg/kg maintenance group, and 131 for the 10-mg/kg group. Patients treated with induction of 5 mg/kg of infliximab at 0, 2, and 6 weeks and then infliximab maintenance, allowing for a dose increase of 5 mg/kg on relapse, displayed a significantly better quality of life throughout the 54 weeks than patients treated with 5 mg/kg at baseline and episodic 5-mg/kg doses on relapse thereafter. More than 50% of the patients in the 3 groups did not reach remission values (170) for IBDQ.

The groups in the ACCENT I study differed greatly concerning the amount of drug they received over the year of treatment. The patients in the group treated episodically received a median of 2.2 active infusions with a median total dose of 9.7 mg/kg. The patients treated with a maintenance dose of 5 mg/kg received a median of 6.7 infusions and a median total dose of 40 mg/kg, whereas the patients treated with a maintenance dose of 10 mg/kg received a median of 6.8 infusions and a median total dose of 64.9 mg/kg.

The Long-Term Course of Luminal Crohn's Disease Treated With Infliximab

Besides the daily symptoms and decreased quality of life, Crohn's disease leads to complications including strictures, abscesses, and fistulas. These complications necessitate admission to the hospital and surgeries and may lead to severe conditions such as short-bowel syndrome. It has been established that more than 60% of the direct costs of Crohn's disease therapy result from hospitalizations and surgeries. Moreover, indirect costs as a

consequence of incapacity to work also are considerable. In the ACCENT I study, significantly fewer Crohn's disease–related hospitalizations occurred in patients in the infliximab 5- and 10-mg/kg scheduled maintenance treatment groups (23 and 24 hospitalizations per 100 patients, respectively) compared with 38 hospitalizations per 100 patients in the group treated with episodic therapy ($P = 0.014$). Moreover, a significantly lower proportion of patients in the 5- and 10-mg/kg scheduled maintenance groups underwent Crohn's disease–related intra-abdominal surgeries (2.9%) as compared with patients treated on an episodic basis with 5 mg/kg (7.4%; $P = 0.01$).[40]

The complications of Crohn's disease occur predominantly as a consequence of inflammation and tissue damage in the gut; therefore, it can be hypothesized that healing of the bowel will result in less complications. In an endoscopic substudy of the Targan trial[27] it was shown that substantial healing of the bowel occurred in parallel with clinical improvement already within 4 weeks of infusion of infliximab.[41] The ACCENT I trial also included an endoscopic healing substudy.[40] Of 99 patients included in that study, 81 (82%) had colonic ulcers (the other patients had only small-bowel involvement) and 74 patients underwent follow-up colonoscopy at 10 weeks, and 58 patients underwent follow-up colonoscopy at week 54, and 36 patients underwent follow-up colonoscopy at both 10 and 54 weeks. At 1 year, 44% of patients treated with maintenance infliximab with access to dose increase had complete mucosal bowel healing (disappearance of all ulcers) as compared with 18% of patients treated with episodic 5 mg/kg of infliximab ($P = 0.041$). The healing rates at 10 and 54 weeks were 25% and 0%, respectively. Patients with complete persistent healing did not require any hospitalizations or surgery.

Infliximab in Fistulizing Crohn's Disease

In fistulizing Crohn's disease a series of 3 infusions with 5 mg/kg of infliximab at weeks 0, 2, and 6 resulted in a response (≥50% reduction of draining fistulas) at 2 consecutive evaluations in 68% of patients treated with 5 mg/kg, in 56% of patients treated with 10 mg/kg, and complete cessation of drainage in 55% and 38% of the patients, respectively.[42] The placebo response rate was 26% and complete response occurred in 13%. The median time to relapse was 12 weeks in the Present et al. study,[42] showing that maintenance therapy is necessary in the majority of patients. In this study the maximal effect of the drug was already achieved by week 6 before the third infusion, suggesting that the loading schedule may not be necessary for induction.

In the ACCENT II study,[43] responders to a loading dose of 5 mg/kg at weeks 0, 2, and 6 (195/282, 69%) were randomized at 14 weeks to 8 weekly infusions of 5 mg/kg of infliximab or placebo. The time to loss of response was significantly longer for patients who received infliximab maintenance (>40 wk) as compared with those who received placebo maintenance (14 wk, $P < 0.001$). At week 54, 19% of placebo maintenance patients had complete absence of draining fistulas compared with 36% of infliximab maintenance patients ($P = 0.009$).

At week 54 the proportion of patients who maintained a response was 23% on placebo and 46% on infliximab maintenance ($P = 0.001$). A total of 61% of the patients who crossed over from placebo to infliximab 5 mg/kg and from 5 to 10 mg/kg because of loss of response reestablished fistula response.

The quality of life of patients with fistulizing Crohn's disease as measured using the IBDQ score at baseline was not greatly diminished (median = 167 for the episodic group, median = 155 for the systematic maintenance group). The IBDQ probably is not the best instrument to pick up the burden of chronic fistulizing Crohn's disease. The median changes from baseline IBDQ at 54 weeks were 5 in the placebo maintenance arm and 10 in the infliximab maintenance patients.

The Long-Term Course of Fistulizing Crohn's Disease Treated With Infliximab

In the ACCENT II study, maintenance with 5 mg/kg infliximab 8 times weekly was associated with a significant decrease in hospitalizations and Crohn's disease–related surgeries but the exact data have not yet been published.

The correlate of mucosal healing in luminal Crohn's disease is the disappearance of internal fistula tracks during therapy. This seems difficult to achieve.

Healing of the fistula tracks during therapy with infliximab has been studied with magnetic resonance imaging[44,45] and endoscopic ultrasonography.[46] Van Assche et al.[44] reported that active inflammation associated with fistula tracks improved greatly short term but that fistula tracks persisted long term with varying degrees of residual inflammation in patients treated episodically with infliximab for perianal fistulizing disease. Similar findings were reported by Bell et al.[45] Both studies also showed that magnetic resonance imaging identified clinically silent sepsis, which may lead to clinical abscesses during therapy. Magnetic resonance imaging follow-up studies long term should be per-

Table 4. Predictors of Response to Infliximab

	Clinical	Genetic	Other
Confirmed	Nonsmoking, concomitant immunosuppression, no stricturing		Increased CRP levels
Not confirmed	Young age, early age onset, short duration, colonic disease, no rectovaginal fistula	LTA haplotype FcGR III a polymorphism	ASCA/pANCA status
No impact	Severity, previous therapies, previous resections	TNF and TNF receptor polymorphisms, NOD2/CARD15	

formed in patients treated systematically with infliximab to investigate whether complete healing of fistula can be achieved and whether this therapy changes the outcome of fistulizing disease long term.

There is little evidence for the efficacy of infliximab for closing rectovaginal fistulas. In an open study from Calgary, the presence of a rectovaginal fistula was a poor prognostic indicator for successful infliximab therapy.[47]

Predictors for Response to Infliximab

Infusion of infliximab 5 mg/kg has a dramatic effect in the majority of patients with refractory luminal and fistulizing Crohn's disease. About 30% of the patients with refractory Crohn's disease consistently have been found to be resistant to infliximab therapy. Moreover, not all other patients are full responders. It is important to find good predictors to select suitable candidates for this treatment and to avoid exposure and possible toxicity in patients who will not benefit from this expensive therapy. The reason for this resistance has not been elucidated. Moreover, there is a loss of response to repeated infliximab infusions in a proportion of patients, which seems unrelated to the immunogenicity associated with the chimeric antibody. Clear risk factors predicting outcome of infliximab therapy have not been identified, although some interesting data have emerged.

The data are summarized in Table 4. Infliximab works best in patients with biologically active inflammation as witnessed by increased CRP levels.[48] Patients with nonstricturing disease[49] who are treated with immunosuppression[36–38] are most likely to respond. The role of smoking as a predictor for disease more refractory to infliximab seems to be confirmed.[37,38] Other clinical parameters are more controversial but 2 studies suggest that colonic disease responds better to infliximab.[36,38] It seems that children with early Crohn's disease have a higher chance of prolonged response to infliximab than children with long-standing Crohn's disease.[50] Besides CRP levels other biomarkers have not been identified clearly as predictors of response to infliximab.[51–56]

Antibodies to Infliximab

Infliximab is a chimeric antibody and is associated with the formation of antibodies to infliximab (ATI), formerly called *human antichimeric antibodies*. The degree of immunogenicity of the antibody is still a matter of debate. The detection of antibodies depends on the sensitivity and on the specifications of the assay used, and the timing of measurement of the antibodies. With the present assays, ATI cannot be measured as long as infliximab is present in the serum of the patient.

Centocor uses a double-antigen enzyme immunoassay in which infliximab serves as detection and capture reagent for the detection of antibodies to infliximab, allowing for detection of all immunoglobulin isotypes and subclasses. Dilutions are reported and not actual concentrations.

In the episodic re-treatment arm of the ACCENT I study[40] the cumulative incidence of antibodies to infliximab as measured with this assay amounted to 30% through 72 weeks, which was significantly higher than the 10% and 7% in the group of patients treated with 8 weekly systematic treatment with 5 mg/kg or 10 mg/kg infliximab infusion, respectively.

In the episodic treatment arm, antibodies to infliximab were associated with a more rapid reduction in serum infliximab concentrations from postinfusion peak levels and a reduction in the magnitude and duration of clinical response. The presence of antibodies to infliximab was associated with an increased rate of infusion reactions and serum sickness–like reactions. However, in the overall population of the trial, similar proportions of antibody-positive, antibody-negative, and inconclusive patients achieved clinical response (64%, 62%, and 65%, respectively) and clinical remission (41%, 39%, and 48%, respectively) at 54 weeks.

In open cohorts of patients treated with infliximab in an episodic on flare manner the formation of antibodies to infliximab was found to be an important clinical problem.

Baert et al.[57] detected antibodies to infliximab in 38 of 125 (61%) patients treated on flare and Farrell et al.[58] reported ATI in 19 of 53 patients (36%) treated also on an on-demand basis. Both investigators used the Prometheus assay. This assay is a microplate enzyme-linked immunosorbent assay based on the double-antigen format in which infliximab is used both during the

solid phase to capture antibodies against infliximab and during the biotinylated detection phase with Neutravidin-horseradish peroxidase. The value is reported in micrograms per milliliter on the basis of calibrations made with affinity-purified polyclonal rabbit anti-mouse IgG F(ab′).

In the studies by Baert et al.[57] and Farrell et al.[58] it was shown clearly that the formation of antibodies to infliximab was associated with the occurrence of infusion reactions and with a shortened duration of response. The formation of ATI was decreased by concomitant therapy with immunosuppressants.

Baert et al.[57] were able to determine a cut-off value of 8 μg/mL for ATI predicting the impact on the key clinical parameters. Patients with antibody titers of 8 μg/mL or greater (37%) had more infusion reactions, decreased response duration, and decreased levels of infliximab 4 weeks postinfusion. Farrell et al.[58] showed that patients receiving prophylactic IV hydrocortisone 200 mg before the first and subsequent infusions of infliximab had lower ATI levels than patients who received placebo prophylaxis.

When infliximab was administered systematically every 8 weeks the negative effects of antibodies to infliximab were counteracted because of the excess of drug over antibodies to infliximab. It is not clear whether systematic re-treatment really suppresses the formation of antibodies to infliximab. However, this regimen also has drawbacks. Once started, how long should the therapy be continued systematically? What will happen if therapy is discontinued because of intercurrent illnesses or bowel surgery for Crohn's disease?

Optimizing Therapy With Infliximab

For (induction) control of luminal disease, one 5 mg/kg IV infusion is efficacious, although a 3-dose induction regimen with IV infusion of 5 mg/kg infliximab at 0, 2, and 6 weeks is somewhat more efficacious. The response rates to these regimens are better when the patients are treated with the correct dose of AZA or methotrexate at the start of infliximab treatment. The odds ratio to response was 2.7 (95% confidence interval: 1.43–5.01) in the large cohort by Vermeire et al.,[36] 7.3 (95% confidence interval: 3.3–10.3) in the study by Arnott et al.[38] for patients taking immunosuppression. Also in the cohort of Parsi et al.,[37] 74% of patients on immunosuppressive therapy responded to infliximab compared with 39% of those not on immunosuppressive therapy ($P = 0.007$). Infliximab can be used in different settings long term. These include infliximab every 8 weeks maintenance as monotherapy, infliximab every 8 weeks combined with immunosuppression maintenance, infliximab episodic with immunosuppression maintenance, and infliximab as a bridge for immunosuppression.

The optimal approach is maintenance with infliximab. If infliximab monotherapy maintenance is used every 8 weeks then infusion of 5 mg/kg is needed with step-up to 10 mg/kg if there is a loss of response. If patients relapse earlier than 8 weeks then the interval must be shortened. It is not clear whether it is beneficial to combine these infusions with maintenance immunosuppression, especially if the patients had failed this therapy previously. More prospective data are needed to answer this question. If for reasons of limited access or cost issues infliximab is used episodically on flare, it is mandatory to use concomitant immunosuppression with AZA (2–2.5 mg/kg/day), 6-MP (1–1.5 mg/kg/day), or methotrexate 15 mg per week intramuscularly or subcutaneously in therapeutic doses to decrease the clinical consequences of immunogenicity of the chimeric antibodies. Moreover, prophylaxis with hydrocortisone before each infusion of infliximab also will decrease the formation of antibodies to infliximab. When the quality of response or the response duration to infliximab infusion decreases this will be caused by high titers of antibodies to infliximab with formation of complexes and early elimination. Increase of the dose administered to 10 mg/kg may restore the efficacy of the drug.

After a drug-free interval of more than 14 weeks, prophylaxis with hydrocortisone before infliximab infusion is recommended to avoid infusion reactions. One should be prepared to treat a delayed hypersensitivity reaction with a high dose (40–60 mg/day) of oral prednisone. Patients who have already suffered such reactions should receive prophylaxis and prolonged glucocorticosteroid treatment. The advantages and disadvantages of systematic maintenance treatment vs. episodic treatment are summarized in Table 5.

Episodic infusions of infliximab sometimes is preferred when this therapy is used as a bridge to allow immunosuppression to kick in. It can be expected that 2–3 infusions will be needed to do the job.

The GETAID (Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives) group[59] is investigating the potential of infliximab as a bridge to immunosuppression. Lemann et al.[59] were not able to show this bridge effect in patients with steroid dependence for more than 6 months. Patients treated with infliximab at 0, 2, and 6 weeks and AZA or 6-MP continued to do better than patients treated with placebo and AZA or 6-MP through 6 months. The rates for remission and off steroids were 83% (infliximab) vs. 41% (placebo) ($P <$

Table 5. Long-Term Treatment Strategies for Treatment of Patients With Crohn's Disease With Infliximab

Episodic therapy	Systematic maintenance therapy
Advantages	Advantages
Room for other therapies	Higher efficacy
Flexibility	No decrease in treatment effect
Lower cost	Standardized
	Decreases immunogenicity effects
	Complete bowel healing possible
	Altering of natural history?
	Monotherapy possible
Disadvantages	Disadvantages
Impact of immunogenicity	Need for dose increase?
Periods of disease activity	Infliximab: forever and ever?
Immunosuppression mandatory	High cost
Only temporary healing	

0.009) for patients naive to immunosuppression and 64% (infliximab) vs. 34% (placebo) ($P = 0.03$) for patients who failed immunosuppression at 12 weeks, and 63% (infliximab) vs. 32% (placebo) ($P = 0.02$) and 50% (infliximab) vs. 26% (placebo) ($P = 0.08$), respectively, at 24 weeks.

For fistulizing Crohn's disease we would advise always using systematic 8-week re-treatment with 5 mg/kg after a loading dose at 0, 2, and 6 weeks. Fistula healing is slow and often incomplete as witnessed by magnetic resonance imaging monitoring studies. Even with systematic reinfusion, response to infliximab often is lost and dose escalations turned out to be necessary. Fistulizing disease, especially perianal disease, necessitates a medical-surgical approach. Many patients will need drainage of abscesses, placement of setons, fistulotomy, advancement flap plasty, and sphincter repair. If setons are in place they should be kept until the first infusions have been administered and then can be removed when maintenance therapy is performed. Unfortunately, a proportion of patients still will undergo proctectomy with definitive stoma.

The cost of biological therapies is high. Infliximab and other anti-TNF antibodies are expensive drugs. Moreover, IV administration is associated with the additional cost of setting up infusion units and for specialized nurses. One way to control costs is by reserving this therapy for patients who have failed conventional immunosuppression. In Europe this is the recommendation and in most European countries the drug is refunded only under this condition. In the United States the drug is used much more liberally.

The cost also can be decreased by using episodic therapy rather than systematic maintenance therapy after induction of response or remission. In the ACCENT I study it was shown that at the end of the study at 54 weeks the differences in response and remission rates were not significantly different for patients treated episodically with infliximab 5 mg/kg as compared with patients treated systematically with 5 mg/kg or 10 mg/kg every 8 weeks. The total amount of drug administered over 1 year was on average 4 times higher for systematic 5 mg/kg maintenance and 6–7 times higher for systematic 10 mg/kg maintenance 8 times/wk as compared with episodic therapy.

We then can calculate the raw total cost for the drug and infusions for the different strategies in the ACCENT I study based on Medicare payment rates including a U.S. $150 cost per infusion and U.S. $650 per 100 mg of infliximab. For episodic therapy the average raw cost can be estimated to be U.S. $3900 over 1 year for a patient of 50 kg and U.S. $6000 for a patient weighing 80 kg. For the systematic 5 mg/kg regimen with step up to 10 mg/kg on loss of response these costs can be estimated to be U.S. $11,800 and 18,400, respectively, and for the 10 mg/kg maintenance regimen with step up to 15 mg/kg on loss of response the costs can be estimated to be about U.S. $23,120 and 36,380, respectively. The average cost to the patient or the insurer may be 1.5–2.0 times the wholesale cost.

The wide range of costs is a consequence of the way the protocol of the ACCENT I study was designed. Cost is an important issue that should be taken into account with any therapy. In assessing cost, however, one must consider not only the cost of the therapy itself, but also the therapy's impact on other drivers of cost, both in terms of direct medical costs and indirect effects of the disease on a patient's ability to be a productive member of society. In moderate-to-severe Crohn's disease, the largest driver of direct cost is hospitalizations and surgeries. Feagan et al.[60] found that 56% of the cost of caring for such patients is derived from hospitalizations compared with only 4% for medications. It has been reported that the mean reimbursements for a Crohn's disease hospitalization in the United States totals almost $22,000.[61] With regard to infliximab, a recent analysis of the data from the ACCENT I study showed that maintenance therapy with this drug was associated with approximately half of the hospitalizations and surgeries that occurred in patients treated with episodic therapy. A previous retrospective analysis from the University of Chicago showed a 66% reduction in emergency room visits, a 43% reduction in endoscopies, a 12% reduction

in radiology studies, and a 16% reduction in outpatient visits after patients began infliximab therapy.[62] Such reductions in the use of health care resources can be expected to result in substantial cost savings that offset the cost of maintenance infliximab therapy. In this regard, Jewell et al.[63] from Oxford recently showed in a prospective study that after adjustment for savings derived from reduced hospital days, the average direct costs per patient for the 6 months after beginning infliximab was £807 and concluded "infliximab is cost-effective for Crohn's disease." In a separate analysis, Wong et al.[64] recently used Markov modeling on ACCENT I data to extrapolate lifetime direct costs of caring for a Crohn's disease patient with different strategies and determined that a regimen of infliximab at a dose of 5 mg/kg every 8 weeks would be expected to result in a net cost savings over the lifetime of a patient. Thus, a substantial amount of the cost of biologic therapies may be balanced by savings in other direct medical costs. Additional savings may be derived from indirect costs (e.g., work attendance and productivity), which have been shown to be an even more significant cost driver in Crohn's disease, probably accounting for twice the amount of direct costs in this disease.[65] It has been difficult to quantify this type of indirect cost, but there is no question that the economic impact of an individual's being able to return to productive work can go a long way toward offsetting the cost of even a very expensive therapy. Clearly, pharmacoeconomic issues are quite complex and must take into account many different variables. Further rigorous analyses are needed before we will be able to accurately assess the true cost (or savings) brought about by biologic therapies in Crohn's disease.

How Long Should We Continue Infliximab Therapy?

There is no controlled study data beyond 1 year but experienced centers already have many patients who have been treated with infliximab for many years. We feel that when the treatment goal is reached in a patient (e.g., the discontinuation of glucocorticosteroids with maintained remission or complete external healing of fistulas), one can try to discontinue infliximab and continue immunosuppression and see whether the disease stays in remission. If the disease relapses, 8 weekly doses of infliximab or episodic therapy can be resumed.

A placebo-controlled infliximab discontinuation study should supply us with important answers to this important question.

Infliximab for UC and Indeterminate Colitis

In Crohn's disease the inflammatory response is characterized by the presence of T-helper 1 cytokines including IL-12, interferon-γ, and TNF, whereas in UC there seems to be an excess of T-helper 2 cytokines including IL-5 and IL-13, whereas IL-12 is lacking. However, interferon-γ is also abundantly present as well as TNF. In UC the presence of IgG plasma cells is remarkable and IgG1 colocalizing with complement C3b can be visualized on the surface of the epithelial cells.

Besides the IgG response, the presence of auto-antibodies to the perinuclear component of neutrophils and epithelial tropomyosin as well as the association with primary sclerosing cholangitis are suggestive of antibody-mediated autoimmunity.

Studies on the use of the monoclonal chimeric IgG1 monoclonal antibody to TNF, infliximab, in UC are scarce and the data are conflicting. Moreover, most studies are uncontrolled. Many systemically acting drugs that work in Crohn's disease (e.g., glucocorticosteroids, immunosuppressive drugs) also are efficacious in UC. Therefore, it was logical to investigate TNF blockade for the treatment of UC.

A first report by Chey[66] on the effect of infliximab in 16 patients with severely active UC refractory to conventional therapy was very provocative. He reported an 88% response rate to infliximab 5 mg/kg clinically, endoscopically, and histologically. Colectomy was avoided in 6 of 7 surgical candidates. Clinical remission was maintained in 14 patients for at least 4 months and in 4 patients for at least 7 months, 6 patients received a second infusion 5 months after the first infusion. Withdrawal of glucocorticosteroid therapy was possible in most patients.

The data published by Su et al.[67] on a multicenter U.S. experience were less dramatic. Of 27 patients with active UC treated with 5 mg/kg infliximab, 12 patients (44%) achieved remission and 6 (22%) had a partial response. In this series fewer patients who were steroid refractory (33%) responded as compared with steroid-responsive patients (83%). Two placebo-controlled trials on the use of infliximab in severe glucocorticosteroid-resistant UC were published. Both studies suffered from small size and lack of statistical power. In the study by Sands et al.,[68] 4 of 8 patients (50%) treated with infliximab responded at 2 weeks and none of the 3 placebo-treated patients responded.

In the study by Probert et al.,[69] remission was achieved with infliximab in 3 of 23 (13%) patients with steroid-refractory UC and in 1 of 19 (5%) patients

treated with placebo at 2 weeks, and the rates were 39% and 30%, respectively, at 6 weeks (NS). These 2 studies do not seem to support the use of infliximab in the management of glucocorticosteroid-refractory UC.

In a recent randomized study reported only in abstract form, Ochsenkuhn et al.[70] investigated the efficacy of infliximab 5 mg/kg at weeks 0, 2, and 6 to induce remission in patients with acute severe UC not refractory to glucocorticosteroids in comparison with high doses of glucocorticosteroids (1.5 mg/kg). Only 13 (6 received infliximab and 7 prednisolone) patients were included in this study. Five of 6 patients responded to infliximab and 6 of 7 responded to prednisolone at 3 and 13 weeks.

Definitive evidence for the role (or no role) of infliximab in the treatment of UC will be offered by the 2 large, ongoing, placebo-controlled, clinical trials ACT 1 and ACT 2.

Data also are scarce for treatment of indeterminate colitis with infliximab. In a retrospective, multicenter, French study[71] the response rate to infliximab in 11 patients with active indeterminate colitis was 50% at day 7 and only 30% at 4 weeks. In this study, 16 of 18 patients (89%) with UC responded at day 7 with complete remission in 50% and a response rate of 61% at 4 weeks. This study suggests that patients with indeterminate colitis are more refractory to infliximab. The results of an open retrospective study reported by Papadakis et al.[72] of infliximab treatment in medically refractory indeterminate colitis were, however, much better. Fourteen of 20 patients (70%) had a complete response to infliximab 5 mg/kg and 2 patients had a partial response. Four of the 14 responders had to step up to 10 mg/kg of infliximab because of attenuation of the response to 5 mg/kg. It was striking that 10 patients who were in the course of follow-up were reclassified as Crohn's disease and 2 as UC.

Anti-TNF Therapy for Systemic Manifestations of IBD

Extraintestinal manifestations occur in up to 40% of patients with IBD. These include mainly skin lesions, eye disease, joint manifestations, and primary sclerosing cholangitis. Many case reports and small series have been published on the use of infliximab for treating extraintestinal manifestations of IBD. Controlled studies are mostly lacking. Regueiro et al.[73] reported on successful treatment of medically refractory pyoderma gangrenosum in 13 patients with IBD. Therapy was efficacious irrespective of the nature of the underlying bowel disease. This is confirmed for all other systemic manifestations of IBD. Moreover, infliximab is efficacious in these disorders also when there is no underlying IBD. Infliximab also seems efficacious for the management of peristomal pyoderma gangrenosum, a particularly disabling complication of Crohn's disease and UC.[74]

Eye abnormalities associated with IBD are episcleritis, scleritis, and uveitis. Uveitis associated with Crohn's disease or UC predominantly is bilateral, posterior, insidious in onset, but chronic in duration. This contrasts with the uveitis associated with spondylarthropathy, which is mostly anterior, unilateral, sudden in onset, and limited in duration.[75] Infliximab is efficacious for treating both types of uveitis.[76,77] Also, etanercept has been reported to be efficacious in chronic active uveitis associated with juvenile-onset RA.[78]

The spectrum of joint disorders associated with IBD includes peripheral arthropathy, which evolves in parallel with the activity of the bowel disease and sacroiliitis or ankylosing spondylitis, which, although associated with IBD, has a rather independent course. Infliximab relieves peripheral joint problems together with the bowel symptoms. Axial manifestations or spondylarthropathy associated with Crohn's disease respond well to infliximab.[79] Moreover, both infliximab and etanercept are very efficacious in improving disease activity, functional indices, and quality of life in patients with active ankylosing spondylitis.[80–82] There are also data suggesting that these strategies prevent functional loss and progress of spine lesions. At present, there are no data available on treatment of primary sclerosing cholangitis with anti-TNF strategies.

Other Anti-TNF Strategies

Infliximab has its established efficacy and safety profile and is the standard to which all other strategies are compared. At present, other antibodies to TNF and receptor proteins are investigated as well as small molecules interfering with the production and action of TNF.

Humanized and Human Antibodies to TNF

It generally is believed, but not proven, that the amount of murine protein present in monoclonal antibodies is related directly to the immunogenicity related to its administration. CDP571 (Humicade; Celltech Slough, UK) is a humanized murine anti-human IgG4 antibody to TNF-α, which has been modified by replacing murine domains not involved in binding with parts of a human IgG4 molecule. The resulting molecule is 95% humanized but still contains 5% mouse epitopes. After a promising pilot trial, CDP571 was tested in a placebo-controlled dose-finding trial.[15] In this study, 169 patients were randomized to receive a single IV dose

of 10 mg/kg, 20 mg/kg, or placebo. At week 2 the rate of clinical response was significantly higher in patients treated with CDP571 (50/111, 45%) compared with placebo (15/56, 27%, $P = 0.023$). Re-treatment was performed either every 8 weeks with placebo or CDP 10 mg/kg or every 12 weeks with placebo or CDP 10 mg/kg (4 groups). The placebo and CDP571 clinical remission rates at 24 weeks were 4% and 11%, respectively, for the every 8 weeks dosing group and 3% and 11%, respectively, for the every 12 weeks dosing groups (NS). In a subsequent, randomized, double-blind, placebo-controlled, multicenter study[83] evaluating the efficacy and tolerability of CDP571 in 396 patients with active Crohn's disease, 34.2% of patients in the active treatment arm showed clinical response at week 2, compared with 21.1% in the placebo arm ($P = 0.011$). Although the response rates at week 28 were higher in the CDP571-treated arm (30.4%) compared with placebo (23.5%), this did not reach statistical significance. In a post hoc exploratory analysis of a subgroup of patients with baseline CRP $>$ 10 mg/L (n = 159), there was a significant difference in the number of patients showing clinical response at week 2 (CDP571, 49.5%; placebo, 15.5%; $P < 0.001$), and at all time points from week 12 to week 28.

Celltech, in cooperation with Pfizer (Cambridge, MA), also is developing CDP-870, a pegylated anti-TNF antibody fragment for the treatment of Crohn's disease. In a placebo-controlled dose-finding study,[84] 291 patients were randomized to placebo, 100 mg, 200 mg, or 400 mg subcutaneously at weeks 0, 4, and 8. The response rates at 12 weeks were 35.6%, 36.5%, 36.1%, and 44.4%, respectively. The differences were not significant. In an exploratory analysis[85] in 119 (41%) patients with increased CRP levels ($\geq$10 mg/L) the differences in clinical response between the 400 mg/dose (53.1%) and placebo (17.9%, $P = 0.005$) were significant at 12 weeks.

Both of these molecules seem extremely safe and less immunogenic than infliximab. Their efficacy is clearly lower than that of infliximab. The question arises whether physicians will want to compromise on efficacy in the scope of better long-term safety. It is to be expected that an important proportion of patients failing CDP-870 will benefit from infliximab.

Adalimumab (Humira; Abbott, Abbott Park, IL) is a fully human anti–TNF-α monoclonal IgG1 antibody. This antibody is as efficacious as infliximab for the treatment of RA. Studies are ongoing in Crohn's disease. Etanercept (Enbrel; Immunex, Wyeth, Madison, NJ) is a human recombinant p75 TNF receptor/IgG fusion protein. This Fc fusion protein is highly effective in treating RA. Although safe, subcutaneous etanercept at a dose of 25 mg twice weekly for the treatment of moderate to severe Crohn's disease was not effective.[86] Onercept (Serono, Geneve, Switzerland), a recombinant, fully human, soluble p55 TNF receptor has shown efficacy in Crohn's disease in an open-label pilot study.[87] A large, placebo-controlled, dose-finding study has been completed but the data have not been published yet. A press release by Serono revealed that the primary endpoint of this trial was not met.

Small Molecules Antagonizing TNF

Thalidomide, a strong anti-emetic and sedative that was withdrawn from the market worldwide in 1961 because of its teratogenicity, has strong anti–TNF-α effects.[88] Thalidomide can down-regulate TNF-α production derived from T lymphocytes, alveolar macrophages, and lamina propria mononuclear cells by interfering with gene transcription or translation.[89] It also can enhance the degradation of TNF-α messenger RNA and inhibits the activation of nuclear factor κ B, the transcription factor that promotes and induces the production of proinflammatory cytokines. In addition to its effects on TNF-α, thalidomide causes a shift from the so-called Th1 to a Th2 cytokine pattern by enhancing the production of IL-4 and IL-5. Finally, an important mechanism of action lies in the inhibition of angiogenesis induced by vascular endothelial-derived growth factor. In 3 pilot trials, 49 patients have now been treated in total.[90–92] Overall, 85% of patients who completed the trials have responded to the treatment, but 27% of patients dropped out owing to side effects. In a follow-up study in 15 patients who had entered remission with infliximab, thalidomide given orally 100 mg/day was effective to maintain remission. Despite the dangers (mainly teratogenicity and peripheral neuropathy) associated with thalidomide, the drug may be useful in a selected subgroup of patients, but if analogues can be developed that lack the adverse effects and maintain or improve the efficacy, these drugs could be of great value.

An interesting approach to down-regulate TNF is the inhibition of mitogen-activated protein kinases, which are signal-transducing enzymes that regulate gene expression and cell proliferation. CNI-1493 is a guanylhydrazone that inhibits the phosphorylation of both p38 mitogen-activated protein kinase and C-Junkinase. This molecule inhibits macrophage activation and the production of the proinflammatory cytokines TNF-α, IL-1, IL-6, MIP-1α, MIP-1β, and also nitric oxide. In a recent study,[93] 12 patients with severe Crohn's disease were assigned randomly to 8 or 25 mg/m^2 CNI-1493 daily for

12 days. Treatment resulted in a significant clinical benefit and rapid endoscopic ulcer healing. A clinical response was seen in 67% of patients at 4 weeks and 58% at 8 weeks. Clinical remission was observed in 25% of patients at week 4 and 42% of patients at week 8. Endoscopic improvement occurred in all but 1 patient. Furthermore, 3 of 6 patients considered infliximab failures showed response with CNI-1493 and 2 of them even entered remission. Fistulae healing occurred in 4 of 5 patients, and steroids were tapered in 89% of patients. CNI-1493 treatment was associated with an inhibition of both JNK and p38 phosphorylation in vitro and with a diminished production of TNF-α. Phase II trials with CNI-1493 and other mitogen-activated protein kinase inhibitors in the treatment of Crohn's disease are ongoing.

Safety of Anti-TNF Strategies in the Treatment of IBD

The ideal drug is efficacious with good safety short as well as long term. The efficacy/safety ratio of a drug can deteriorate over time owing to several reasons. The efficacy may decrease with increased risk for adverse events. This is the case for glucocorticosteroids in the treatment of IBD. For other drugs, efficacy may remain unchanged but the rate of side effects may increase. This is the case for antibiotics in the treatment of perianal fistulizing Crohn's disease and for chronic pouchitis. For infliximab it seems that efficacy decreases over time because up to 50% of patients may need step up of dose although safety seems good in the long term.

Toxicities related to biological therapies can be classified into 3 categories. Toxicity may be disease specific (e.g., the occurrence of abdominal sepsis associated with Crohn's disease of the bowel). Other adverse events may be class specific, including the risk for intracellular infection (e.g., tuberculosis), demyelinating disease, worsening of congestive heart failure, or lymphoma. Finally, toxicity may be molecule specific. IgG1 antibodies are associated more with auto-immunity than IgG4 antibodies. Immunogenicity associated with antibody therapy is probably more important for chimeric as compared with humanized or human antibodies. IgE-mediated allergic reactions are drug and host specific. Small molecules have a greater risk for associated teratogenicity than large antibodies.

Safety assessment in drug development is difficult. Clinical trials have the advantage of including placebo-treated control groups and meta-analysis of trials is mostly able to pick up increases in rather common events such as infusion reactions and upper respiratory tract infections. Controlled trials, however, involve relatively few patients with strict inclusion criteria and with limited follow-up evaluation (1–3 yr). In contrast, postmarketing surveillance has the advantage of large numbers of patients who are treated for variable durations of time. Moreover, patients usually not included in trials such as children or elderly patients are exposed to drugs postmarketing. The disadvantage of this type of adverse-events reporting is that there is no control population or denominator and that reporting rates and accuracy are highly variable. Postmarketing surveillance is more likely to pick up serious but low-background events. For infliximab this was the case for tuberculosis.

Another confounding factor is cumulative toxicity of multiple treatments in IBD. The risk for sepsis, opportunistic infections, malignancies, and myelosuppression is much greater if biologicals are administered on a background of glucocorticosteroids and/or immunosuppression. The rate of serious infections in clinical trials in Crohn's disease and RA in patients treated with infliximab (6.2%) was not higher than in patients treated with placebo (6.8%) (Periodic Safety Update Report). The mortality rate in the clinical trials with 3 years post-study follow-up evaluation was 1.7% for patients treated with infliximab and 4.2% for placebo-treated patients. Reports of infection-related mortality must be interpreted with caution because a number of patients in such observational studies often have been treated for off-label life-threatening conditions.[94] In a large cohort study[95] in 500 consecutive patients treated at the Mayo Clinic, infliximab-related infections were found in 8.2% including 20 patients with serious infections: 2 patients had fatal sepsis, 8 patients had pneumonia (2 were fatal), 6 patients had viral infections, 2 patients had abdominal abscess, 1 patient had cellulitis, and 1 patient had histoplasmosis.

The issue of antibodies to infliximab and its relation with infusion reactions and loss of response was discussed previously.

Acute infusion reactions usually are managed easily by temporarily interrupting the infusion and administration of hydrocortisone 100–250 mg IV. The infusion is resumed after resolution of the infusion reaction at a slower rate. In patients who already have suffered previous infusion reactions, prophylactic antihistamine and hydrocortisone 30 minutes before each subsequent infusion can prevent new infusion reactions.

Severe serum sickness–like reactions have been observed in Crohn's disease patients 3–12 days after infliximab when this therapy was reinstituted after a long drug holiday. In a study by Hanauer et al.,[96] this delayed infusion reaction occurred in 25% of patients re-treated

after an interval of at least 2 years since the previous administration of infliximab. Symptoms associated with these reactions included fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema, and/or dysphagia. These reactions were associated with a marked increase in antibodies to infliximab, a loss of detectable serum concentrations of infliximab, and a loss of drug efficacy. These symptoms are readily controlled by high doses of IV or oral glucocorticosteroids.

Infliximab has been associated with adverse outcomes in patients with congestive heart failure, and should be used in patients with congestive heart failure only after consideration of other treatment options. The results of a randomized study[97] evaluating the use of infliximab in patients with heart failure (New York Heart Association functional class III/IV) suggested higher mortality in patients who received 10 mg/kg infliximab, and higher rates of cardiovascular adverse events at doses of 5 and 10 mg/kg. There have been postmarketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking infliximab. There also have been rare postmarketing reports of new-onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been less than 50 years of age. If a decision is made to administer infliximab to patients with heart failure, they should be monitored closely during therapy, and infliximab should be discontinued if new or worsening symptoms of heart failure appear.

Infliximab and other agents that inhibit TNF have been associated in rare cases with optic neuritis, seizure, and new-onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis.[98] Infliximab therapy frequently is associated with autoimmunity with the formation of antinuclear antigens and antibodies to double-stranded DNA. Drug-induced lupus reactions without end-organ damage occur rarely. Antinuclear antibodies are associated with female sex and with the occurrence of papulosquamous or butterfly rash.[99] Patients with these antibodies can be re-treated safely with infliximab without increased risk for complications. Reactivation of latent tuberculosis is a severe complication with all anti-TNF strategies.[100] By February 2003, active TB was reported in 350 of more than 400,000 patients treated with infliximab or a cumulative incidence of 0.46 per 1000 patient-years. Most cases occurred within the first 2 months after initiation of therapy. The cumulative mortality amounted to 9%.

All patients who will undergo treatment with an anti-TNF agent should be evaluated for latent tuberculosis with a tuberculin test and chest radiograph. Treatment of latent tuberculosis should be initiated before therapy with infliximab. Recommendation for tuberculosis screening and treatment are proposed by national scientific organizations and authorities.

In the Crohn's disease and RA trials 6 lymphomas were diagnosed for a follow-up of 4148 patient-years vs. 0 for 691 placebo patient-years. All lymphomas occurred in patients treated with concomitant immunosuppression. Four of these lymphomas occurred in patients with RA. In RA the background incidence of lymphoma is increased in comparison with the general population. By February 2003, lymphoma was reported spontaneously in 71 cases (45 in RA and 20 in Crohn's disease patients) with approximately 365,000 patients treated. The trial and postmarketing surveillance data do not suggest an increased risk for lymphoma in patients treated with Remicade. Likewise, the incidence of nonlymphoma malignancies does not seem increased. One should be cautious, however, because the duration of follow-up of patients with RA and Crohn's disease treated with infliximab is limited.

Anti-TNF Strategies in IBD: Conclusions

The advent of infliximab for the treatment of Crohn's disease has been very beneficial for our patients. The ideal strategy, however, would be a small oral molecule with similar efficacy but lacking the drawbacks of the parenteral administration route and the problems of immunogenicity. Clinical development of different compounds including antibodies and small molecules is currently ongoing and the clinicians look forward to even better drugs with which to treat their patients.

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Address requests for reprints to: Paul Rutgeerts, M.D., Ph.D., F.R.C.P., Department of Medicine, Division of Gastroenterology, University Hospital Gasthuisberg, Herestraat 49, Leuven 3000, Belgium. e-mail: paul.rutgeerts@uz.kuleuven.ac.be; fax: (32) 16-34-44-19.