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A SPECIAL MEETING REVIEW EDITION

Highlights in Crohn's Disease and Ulcerative Colitis

Digestive Disease Week 2012
May 19–22, 2012 • San Diego, California

Special Reporting on:

- Safety and Efficacy of Subcutaneous Golimumab Induction Therapy in Patients with Moderately to Severely Active UC: PURSUIT-SC
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PLUS Meeting Abstract Summaries

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A Phase II/III Randomized, Placebo-Controlled, Double-Blind Study to Evaluate the Safety and Efficacy of Subcutaneous Golimumab Induction Therapy in Patients with Moderately to Severely Active Ulcerative Colitis: PURSUIT-SC

Over the past several years, the role of tumor necrosis factor α (TNF-α) in the pathogenesis of ulcerative colitis (UC) has become more firmly established, with a wide variety of data from both preclinical and clinical settings providing evidence of its importance in the disease process. Based on this knowledge, numerous agents that inhibit TNF-α have been tested for the treatment of UC, and some of these agents have gained approval from the US Food and Drug Administration (FDA).

One new anti–TNF-α agent, golimumab, is different from other monoclonal anti–TNF-α antibodies in that it targets a unique epitope on the TNF-α molecule. Preclinical studies have demonstrated that golimumab binds with high affinity to both the soluble and membrane-bound forms of TNF-α.[1] Further, studies have shown that golimumab is superior to other anti–TNF-α antibodies in terms of its ability to inhibit both TNF-α–mediated cytotoxicity and TNF-α–mediated endothelial cell activation.

A human monoclonal antibody directed against TNF-α, golimumab is currently approved for the treatment of rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis—all conditions in which TNF-α has been implicated, and golimumab is currently being evaluated as a possible treatment for UC. At the 2012 Digestive Disease Week (DDW) Meeting, held May 19–22, 2012 in San Diego, California, William Sandborn presented results of the PURSUIT-SC study, a clinical trial that evaluated the safety and efficacy of golimumab as induction therapy for the treatment of moderate-to-severe UC.[2]

PURSUIT-SC was a randomized, placebo-controlled, double-blind, phase II/III trial that enrolled UC patients who were naïve to anti–TNF-α therapy. Enrolled patients had moderately to severely active UC (as defined by a Mayo clinic score of 6–12 with an endoscopy subscore of 2 or 3) and were either receiving adequate treatment (including 6-mercaptopurine, azathioprine, corticosteroids, and/or 5-aminosalicylate acid), had previously failed to respond to or tolerate treatment with these agents, or were corticosteroid dependent.

The design of the PURSUIT-SC trial was unique in that it began as a phase II dose-ranging study, after which patients were integrated into the confirmatory phase III portion of the study. During the dose-ranging portion of the study, patients were randomized to 1 of 4 arms: placebo, 100/50 mg golimumab (100 mg at Week 0 and 50 mg at Week 2), 200/100 mg golimumab (200 mg at Week 0 and 100 mg at Week 2), or 400/200 mg golimumab (400 mg at Week 0 and 200 mg at Week 2). During the phase III portion of the study, only the 200/100 mg and 400/200 mg doses of golimumab were used. Golimumab was administered subcutaneously in all groups.

The primary endpoint of the study was clinical response at Week 6, which was defined as a decrease in the Mayo clinic score of at least 30% and at least 3 points from baseline, with either a decrease in the rectal bleeding subscore of at least 1 point from baseline or a rectal bleeding subscore of 0 or 1. Secondary endpoints included clinical remission (defined as a Mayo clinic score ≤2 with no individual subscore >1), mucosal healing (defined as a Mayo clinic endoscopic subscore of 0 or 1), and change from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) score, all assessed at Week 6.

A significantly higher proportion of patients in the golimumab treatment groups attained the primary endpoint of clinical response at Week 6 compared to the placebo group (51.8% and 55.0% in the 200/100 mg golimumab and 400/200 mg golimumab arms, respectively, vs 29.7% in the placebo arm; $P<.0001$ for both comparisons vs placebo). A highly significant difference also emerged in terms of the proportion of patients who achieved clinical remission at Week 6 (6.3% in the placebo group vs 18.7% in the 200/100 mg golimumab group and 17.8% in the 400/200 mg golimumab group; $P<.0001$ for both comparisons vs placebo) and mucosal healing at Week 6 (28.5% in the placebo group vs 43.2% in the 200/100 mg golimumab group and 45.3% in the 400/200 mg golimumab group; $P=.0005$ and $P<.0001$, respectively). The mean change from baseline in IBDQ scores at Week 6 was 14.6 points in the control group versus 27.4 points in the 200/100 mg golimumab group and 27.0 points in the 400/200 mg golimumab group (P<.0001 for both comparisons vs placebo).

The PURSUIT-SC study also evaluated the overall phase II/III trial population through Week 6 to assess the safety profile of golimumab; this analysis included a total of 1,065 patients. The total proportion of patients who experienced an adverse event was 38.2% in the placebo group versus 39.1% for the combined golimumab group. The number of patients

who experienced a serious adverse event was also relatively similar in both groups (6.1% in the placebo group vs 3.0% in the combined golimumab group). Rates of adverse events and serious adverse events were similar between the 200/100 mg golimumab and 400/200 mg golimumab groups. Malignancies were rare in all groups, occurring at rates of 0.3%, 0%, and 0.3% in the placebo, 200/100 mg golimumab, and 400/200 mg golimumab groups, respectively. Injection site reactions were also rare and occurred at similar rates across golimumab dosage groups. One death occurred in a patient in the 400/200 mg golimumab arm, and demyeliniation (a well-described toxicity of anti–TNF-α therapy) was reported in 1 patient in the 400/200 mg golimumab arm.

In conclusion, the PURSUIT-SC study showed that golimumab produced clinical response and remission by Week 6, induced mucosal healing, and improved health-related quality of life. Further, the safety profile of golimumab when used for the treatment of UC proved relatively similar to the safety profile observed when golimumab is used for the treatment of rheumatologic conditions, as well as the safety profile observed with other anti–TNF-α drugs.

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The Future of IBD Therapy: Individualized and Optimized Therapy and Novel Mechanisms

In a Presidential Plenary lecture at the 2012 DDW meeting, William Sandborn summarized several recent advances in the treatment of inflammatory bowel disease (IBD). Many of these advances relate to individualized therapeutic strategies for patients with UC and Crohn's disease (CD).

Customized Drug Dosing

One of the major trends that will define the future of IBD therapy is the increased use of pharmacokinetics to customize drug dosing for individual patients. Monoclonal antibody therapeutics are especially susceptible to factors that affect their pharmacokinetic characteristics.[1] For example, the presence of antidrug antibodies (ADAs) decreases the serum concentration of therapeutic monoclonal antibodies and can cause a 3-fold increase in the clearance of the therapeutic antibody. Notably, clinical studies of IBD patients treated with monoclonal antibodies demonstrate that patients with detectable ADAs have worse clinical outcomes than patients who do not develop ADAs.

Another factor that affects the pharmacokinetic characteristics of monoclonal antibodies is the concomitant use of immunosuppressant therapy, which has been shown to reduce formation of ADAs, increase the serum concentration of the therapeutic monoclonal antibody, and decrease its clearance. IBD patients who are receiving monoclonal antibody therapies plus concomitant immunosuppressant therapy often have improved clinical outcomes compared to patients who receive the antibody alone.

Finally, increased clearance of therapeutic monoclonal antibodies—which results in decreased serum concentrations of the antibody—has been associated with high baseline serum concentration of TNF-α, low serum albumin levels, and high baseline levels of the inflammatory marker CRP. Certain patient-related factors have also been shown to impact the pharmacokinetics of therapeutic monoclonal antibodies, including high body mass index and male sex, both of which may increase clearance.

The relationship between serum concentrations of the therapeutic monoclonal antibody and clinical outcomes was recently demonstrated in an analysis of the ACT-1 and ACT-2 studies.[2] In this analysis, patients from these 2 trials were pooled and divided into quartiles according to serum infliximab concentrations; the proportion of patients with a clinical response at Week 8 was found to increase with increasing serum concentration of infliximab. Only 33.2% of placebo-treated patients achieved a clinical response at Week 8 compared to 52.6%, 69.0%, 75.4%, and 81.0% of patients in the 1st, 2nd, 3rd, and 4th infliximab serum concentration quartiles, respectively. Similarly, 13.1% of placebo-treated patients achieved clinical remission at Week 30 compared to 14.6%, 25.5%, 59.6%, and 52.1% of patients in the 1st, 2nd, 3rd, and 4th infliximab serum concentration quartiles, respectively.

New Treatment Endpoints

Another important trend in treatment for IBD is the evolution of treatment endpoints from resolution of symptoms to mucosal healing,

ABSTRACT SUMMARY Efficacy and Safety of Budesonide MMX 6 mg for the Maintenance of Remission in Patients With Ulcerative Colitis: Results From a Phase III, 12-Month Safety and Extended Use Study

Two studies presented at the DDW 2012 meeting examined budesonide MMX, a novel formulation of the nonsystemic corticosteroid budesonide that is designed to deliver active drug to the colon.[1,2] A 12-month, placebo-controlled, phase III, extended-use study was conducted to evaluate the efficacy and safety of budesonide MMX for maintenance of remission in patients with UC. Patients received induction therapy with 9 mg budesonide MMX in either a phase III induction trial or an open-label study, after which 122 patients who were in clinical and endoscopic remission were randomized to 12 months of maintenance treatment with either placebo or 6 mg budesonide MMX once daily. Clinical remission following induction therapy was defined according to the following criteria: UC disease activity index (UCDAI) score no greater than 1 point after 8 weeks, no rectal bleeding, normal stool frequency, no mucosal friability at full colonoscopy, and a greater-than-1 point reduction from baseline in endoscopic score. Maintenance of remission during this extended study was defined as UCDAI subscores of 0 for both rectal bleeding and stool frequency.

While this trial was not powered to show statistical significance, an exploratory evaluation determined the proportion of patients who were in clinical remission after 1, 3, 6, 9, and 12 months (and/or the end of study/early withdrawal visit). A safety analysis was also conducted at each of these time points. In addition, time to clinical relapse was assessed as a secondary endpoint; this endpoint was defined as the time in days until the recurrence of rectal bleeding or stool frequencies at least 1–2 stools/day greater than normal for the patient.

In one poster presented at the 2012 DDW meeting, William Sandborn and colleagues presented efficacy results of this study.[1] This analysis demonstrated that the proportion of patients who maintained remission with budesonide MMX was not significantly different than the proportion of patients who maintained remission with placebo. This lack of difference was potentially due to insufficient statistical power. However, the probability of clinical relapse at 12 months was significantly decreased in the budesonide MMX arm compared to the placebo arm (intent-to-treat population, 40.9% vs 59.7%, respectively; P=.0224). Additionally, analysis of the the intent-to-treat population showed that the median time to clinical relapse was significantly prolonged with budesonide MMX versus placebo (log-rank test P=.0224).

Safety results from this phase III trial were presented by Simon Travis and colleagues in a separate poster.[2] This safety analysis included data from 123 patients. The rate of treatment-related adverse events was similar between the budesonide MMX arm and the placebo arm (21.0% vs 21.3%, respectively). The most frequent adverse events were colitis ulcerative, osteopenia, Cushing syndrome, abdominal pain, flushing, and hirsutism. Only 1 patient in each arm reported a serious adverse event, neither of which were related to the study drug. There were no deaths or life-threatening events during the study. Finally, the overall incidence of potential glucocorticoid effects was similar between budesonide MMX–treated patients and placebo-treated patients (14.5% vs 11.5%, respectively); these side effects included moon face, striae rubrae, flushing, fluid retention, mood and sleep changes, insomnia, acne, and hirsutism.

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prevention of structural damage, and prevention of disability. Colombel and colleagues recently demonstrated an association between mucosal healing at Week 8 and time to colectomy among infliximab-treated patients.[3] Significantly fewer patients with a Mayo clinic endoscopy subscore of 0 or 1 required colectomy or commercial infliximab use compared to patients with an endoscopy subscore of 2 or 3 (P<.0001). This same study showed a significant association between Mayo clinic endoscopy subscore at Week 8 and corticosteroid-free symptomatic remission at Week 30 during treatment with anti–TNF-α antibody therapy (P<.001). The rate of Week 30 corticosteroid-free symptomatic remission was 46% among patients with a Mayo clinic endoscopy subscore of 0 at Week 8 versus 34%, 11%, and 6.5% for patients with endoscopy subscores of 1, 2, and 3, respectively.

By using deep remission as a treatment endpoint for CD, clinicians are aiming to manage the patient's disease in a way that addresses the underlying disease process, rather than just controlling symptoms. For patients with no bowel damage or disability, the goal of achieving deep remission is to prevent damage and disability; in these patients,

deep remission is defined as resolution of 1 or more objective measures of inflammation (monitored via endoscopy, biomarkers, or imaging) and resolution of symptoms. For patients who already have existing bowel damage or disability, the goal of achieving deep remission is to prevent further damage and disability and to reverse damage, if possible; in this group, the definition of deep remission is the resolution of 1 or more objective measures of inflammation (monitored via endoscopy, biomarkers, or imaging) and improvement of symptoms, if possible.

The importance of achieving deep remission was demonstrated in an analysis of the EXTEND trial.[4,5] In this study, deep remission was defined as clinical remission (Crohn's disease activity index [CDAI] score <150 points) and complete mucosal healing. None of the 11 patients who achieved deep remission with adalimumab at Week 12 required hospitalization through Week 52; in comparison, the rate of all-cause hospitalization among patients who did not achieve deep remission at Week 12 was 17% (9 of 53 patients). The same trend was observed for CD-related hospitalization through Week 52, which occurred in 0% and 9% of patients with and without deep remission, respectively.

A number of measures have now been developed to help clinicians assess the extent of bowel damage and disability. Parente and colleagues recently published a newly developed CD Digestive Damage Score, called the Lémann score, which can be used to map a patient's disease course on a double-axis graph.[6] In this graph, time is shown on the x-axis, digestive damage is on the left y-axis, and inflammatory activity is on the right y-axis; the slope of the line connecting the data points gives a measure of disease progression. Further, Peyrin-Biroulet and colleagues recently reported the development of the first disability index for IBD, which is based on the international classification of functioning, disability, and health.[7] A total of 19 core set categories were used to develop the index: 7 for body functions, 2 for body structures, 5 for activities and participation, and 5 for environmental factors.

Combination Therapy and New Agents

Another important trend in the treatment of IBD is the shift from single-agent azathioprine therapy to combination therapy. Data from Sans and colleagues showed that the early use of azathioprine in patients with recently diagnosed CD can have a corticosteroid-sparing effect.[8] Further, the SONIC trial demonstrated the safety and efficacy of infliximab and azathioprine given prior to immunosuppressive or biologic therapy; this trial randomized 508 CD patients with moderate-to-severe disease to single-agent azathioprine therapy, infliximab monotherapy, or combination therapy with both drugs.[9] The SONIC trial was the first study to conclusively show that infliximab monotherapy yielded higher rates of corticosteroid-free clinical remission (assessed at Week 26) than single-agent azathioprine therapy (44.4% vs 30%, P=.009). SONIC also showed that these rates could be further increased when infliximab and azathioprine were used in combination (56.8%; P=.022 for combination therapy vs infliximab monotherapy; P<.001 for combination therapy vs single-agent azathioprine therapy).

Finally, several advances in the treatment of IBD are related to the discovery of novel biologic targets. One such target is the $\alpha 4\beta 7$ integrin, which is targeted by the gut-specific humanized monoclonal antibody vedolizumab (MLN0002). This drug has unique pharmacologic properties that confer specificity and selectivity for treatment of IBD, and previous phase II trials have demonstrated that vedolizumab is active for the treatment of both CD and UC.[10-12]

Building on these studies, a phase III study of vedolizumab was recently conducted, and the results of this study were reported by Brian G. Feagan during the 2012 DDW meeting.[13] This study was a randomized, placebo-controlled, double-blind, multicenter, phase III trial that assessed the activity of vedolizumab in patients with treatment-refractory, moderately to severely active UC. A total of 374 patients were enrolled in this study; patients had a mean age of 40.5 years and a mean disease duration of 6.5 years. Patients were randomized to receive with either 300 mg intravenous vedolizumab or placebo on Days 1 and 15.

All 3 of the efficacy endpoints assessed at Week 6 revealed significant improvements among patients treated with vedolizumab compared to patients who received placebo. Rates of clinical response were 47.1% for vedolizumab versus 25.5% for placebo (P<.001), rates of clinical remission were 16.9% and 5.4%, respectively (P=.0009), and rates of mucosal healing were 40.9% and 24.8%, respectively (P=.0012). Among patients who had previously received treatment with an anti–TNF-α agent, rates of clinical response were 39% for vedolizumab-treated patients versus 20.6% for the placebo group; these rates increased to 53.1% and 26.3%, respectively, among patients who were naïve to anti–TNF-α agents.

Another target under active investigation for the treatment of IBD is interleukin (IL) 12/23p40, which is targeted by the humanized monoclonal antibody ustekinumab. This antibody binds specifically to the p40 protein subunit that is shared by both IL-12 and IL-23, 2 cytokines whose immune system activity has been implicated in the pathogenesis of CD and other autoimmune disorders.[14]

In a study presented at DDW 2011, ustekinumab was evaluated in 526 CD patients who were randomized to receive either placebo or 1 of 3 doses of ustekinumab (1 mg/kg, 3 mg/kg, or 6 mg/kg) given as a single intravenous

infusion.[15] All patients had active disease and were resistant to or intolerant of previous anti–TNF-α therapy. This study found that significantly more ustekinumab-treated individuals achieved a clinical response at Week 6 compared to patients who received placebo (36.8% vs 23.5%; *P*=.005). These differences remained significant across dosage groups, with clinical response at Week 6 being achieved by 36.6% of patients in the 1 mg/kg ustekinumab group (*P*=.021), 34.1% of patients in the 3 mg/kg ustekinumab group (*P*=.057), and 39.7% of patients in the 6 mg/kg ustekinumab group (*P*=.005; all comparisons versus placebo). After the initial ustekinumab infusion, patients were re-randomized to receive either placebo or 90 mg subcutaneous ustekinumab at Weeks 8 and 16. Early in therapy, the rate of clinical remission did not show a significant difference between placebo and ustekinumab; however, this difference became greater with continued ustekinumab treatment. The rate of clinical remission at Week 22 was 41.7% with ustekinumab versus 27.4% with placebo (*P*=.029).

A third target being pursued for treatment of IBD is the Janus kinase (JAK). Acting via JAK inhibition, the new drug tofacitinib modulates signaling of several proinflammatory cytokines. Tofacitinib was recently evaluated in a multicenter, double-blind, phase II clinical trial that used model-fitted clinical response rates at Week 8 as its primary efficacy endpoint.[16] A total of 194 patients with moderate-to-severe UC, a Mayo score of 6 or higher, and an endoscopic subscore of 2 or higher were enrolled in this study; patients were randomized to placebo or 1 of 4 doses of tofacitinib (0.5 mg, 3 mg, 10 mg, or 15 mg) twice daily for 8 weeks. The estimated clinical response rate with placebo was 38.1%; this rate increased steadily with increasing dosage of tofacitinib, with response rates of 39.4%, 46.1%, 65.0%, and 76.3% among patients in the 0.5 mg, 3 mg, 10 mg, and 15 mg tofacitinib groups, respectively. At a dose of 10 mg twice daily, tofacitinib resulted in a 26.9% increase over placebo in the estimated clinical response rate at Week 8 (90% confidence interval [CI], 17.0–36.8); at 15 mg twice daily, a 38.2% increase over placebo was observed (90% CI, 25.3–51.2).

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Infliximab Concentration and Clinical Outcome in Patients with Ulcerative Colitis

The ACT-1 and ACT-2 studies were multicenter, randomized, double-blind, placebo-controlled trials that compared 5 mg/kg and 10 mg/kg doses of infliximab versus placebo for the treatment of moderate-to-severe UC.[1] Each study enrolled 364 patients between March 2002 and March 2005, and all patients had a Mayo clinic score of 6–12 points. Treatment was administered at Weeks 0, 2, and 6, followed by maintenance therapy every 8 weeks through Week 22 in ACT-2 and through Week 46 in ACT-1. The primary study endpoint was clinical response at Week 8; secondary endpoints included clinical response or remission with discontinuation of corticosteroids at Week 30 in both studies (and at Week 54 in ACT-1), clinical remission and mucosal healing at Weeks 8 and 30 in both studies (and at Week 54 in ACT-1), and clinical response at Week 8 in patients with steroid-refractory disease. In both studies, clinical response was defined as a decrease in the Mayo clinic score of at least 3 points and at least 30%, with an accompanying decrease of at least 1 point in the rectal bleeding subscore or an absolute rectal bleeding subscore of 0 or 1.

Significantly more patients in both the 5 mg/kg and 10 mg/kg infliximab groups achieved clinical response at Week 8 compared to patients in the placebo arm (69% and 62% vs 37%; $P<.001$ for both comparisons vs placebo). In both trials, infliximab-treated patients were more likely to achieve clinical response at Week 30 ($P\leq.002$ for all comparisons). ACT-1, which had a longer follow-up period, also showed that more of the patients treated with infliximab (either 5 mg/kg or 10 mg/kg) achieved a clinical response at Week 54 (46% and 44%, respectively) compared to patients who received placebo (20%; $P<.001$ for both comparisons).

Building on this research, a post–hoc analysis of the ACT-1 and ACT-2 studies was conducted to evaluate the association between serum infliximab concentrations and clinical outcomes in patients with moderately to severely active UC; Walter Reinisch presented results of this post–hoc analysis during the 2012 DDW meeting.[2] While the ACT studies examined 2 doses of infliximab, the post–hoc analysis only evaluated patients in the 5 mg/kg infliximab dosage group, as this is the dose that was approved by the FDA as a treatment for UC.

Pharmacokinetic sampling was performed throughout the ACT-1 and ACT-2 studies, most often at the time of an infusion, although samples

ABSTRACT SUMMARY The Prevalence of Human Antichimeric Antibodies in Patients on Infliximab Increases with Age

In another poster presented at the 2012 DDW meeting, David Barry and Richard S. Bloomfeld reported on a study in which they determined the prevalence of human antichimeric antibodies among infliximab-treated IBD patients and correlated the presence of these antibodies with patient age.[1] In this retrospective analysis, all human antichimeric antibody testing performed by Prometheus Laboratories between November 2000 and January 2011 was evaluated. A total of 26,450 patients were included in this analysis; individuals younger than 10 years and older than 80 years of age were excluded. Patients were divided into 7 age groups, with each group spanning a range of 10 years. A negative human antichimeric antibody result was defined as a serum concentration below 1.69 µg/mL, while a positive result was defined as a serum concentration above 1.69 µg/mL.

The proportion of patients with a negative human antichimeric antibody result decreased significantly with increasing patient age (Chi square; $P<.0001$). Of the 10,155 patients aged 10–19 years, 81.9% had a negative human antichimeric antibody result. This percentage decreased to 80% of 4,004 patients aged 20–29 years, 78.9% of 3,831 patients aged 30–39 years, 79.9% of 3,509 patients aged 40–49 years, and 79.9% of 2,735 patients aged 50–59 years. This number continued to decrease in older patients, with 77.8% of patients aged 60–69 years and 74.8% of patients aged 70–79 years having a negative human antichimeric antibody result.

Based on these data, the investigators concluded that human antichimeric antibodies increase in prevalence among older infliximab-treated IBD patients. This finding could have a significant impact on clinical decision-making in young versus older IBD patients who lose response to anti–TNF-α therapy.

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were also taken at Week 8. By Week 8, the subset of UC patients who were responding to infliximab began to diverge from the group of patients who did not respond to infliximab. Interestingly, there was no significant difference in peak serum infliximab levels between the responding and nonresponding patients at this time point. In contrast, trough infliximab levels were lower in nonresponding patients versus responding patients.

Further analysis demonstrated that patients who achieved a clinical response at Week 8 had a serum infliximab concentration of 35 µg/mL, compared to a serum infliximab concentration of 25.8 µg/mL in patients who did not achieve a clinical response; this difference was statistically significant. Similarly, patients who achieved and did not achieve mucosal healing by Week 8 had serum infliximab concentrations of 36.1 µg/mL and 26 µg/mL, respectively; this difference did not achieve statistical significance.

At Week 30, trough infliximab concentrations were again higher among patients who achieved a clinical response compared to those who did not (5 µg/mL vs 1.2 µg/mL). Interestingly, there was a large amount of variability in serum infliximab concentrations between responders and nonresponders and between patients who achieved mucosal healing and those who did not. At the time of the Week 30 trough level measurement, this separation increased further. This finding could be attributed to the increased rate of drug clearance due to development of immunogenicity. When serum infliximab concentrations were divided into quartiles, Reinisch and colleagues found that there was an incremental increase in the likelihood of achieving clinical response or mucosal healing with each higher quartile of infliximab concentration; the same trends were shown for clinical remission at Weeks 30 and 54.

From this post–hoc analysis, the investigators concluded that serum infliximab concentrations began to diverge as early as Week 8 between patients who achieved an endpoint (either clinical response or mucosal healing) and those who did not. While the serum infliximab concentrations required to achieve response and maintain remission varied substantially among patients, higher serum infliximab concentrations were associated with a greater likelihood of achieving these endpoints. The investigators acknowledged that a prospective study is needed to determine whether adjustment of serum infliximab concentrations has clinical utility for optimizing patient outcomes.

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Vedolizumab Induction Therapy for Ulcerative Colitis: Results of GEMINI I, A Randomized, Placebo-Controlled, Double-Blind, Multicenter, Phase III Trial

Given the limitations of current therapies for UC, novel therapeutic strategies with new mechanisms of action are needed. One such agent is vedolizumab, a novel, gut-selective, monoclonal antibody directed against the α4β7 integrin, which induces selective inhibition of lymphocytic trafficking in the gut. This selective inhibition offers a possible advantage over the more systemic effects elicited by natalizumab, which inhibits both the α4β1 the α4β7 integrins.

At the 2012 DDW meeting, Brian Feagan presented the results of a randomized, placebo-controlled, double-blind, multicenter, phase III trial designed to determine the long-term efficacy and safety of vedolizumab when given as induction therapy for UC.[1] All patients in this study had moderately to severely active UC and had failed at least 1 prior therapy. The intent-to-treat population for the induction phase of this study consisted of 374 patients with active UC. All patients had a Mayo clinic score of 6 or higher and an endoscopic subscore of 2 or higher despite treatment with corticosteroids, purine antimetabolites, and/or anti–TNF-α agents. Patients were randomized 3:2 to treatment with vedolizumab or placebo; vedolizumab was administered as a 300-mg intravenous dose on Days 1 and 15.

The primary study endpoint for the induction phase of the study was clinical response at Week 6; clinical response was defined as a reduction in the total Mayo clinic score of at least 3 points and a decrease from baseline of at least a 30% plus a decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore no greater than 1. Secondary endpoints for the induction phase of the study included mucosal healing

and clinical remission. Clinical remission was defined as a total Mayo clinic score no greater than 2 points with no individual subscore greater than 1; mucosal healing was defined as a Mayo endoscopic subscore no greater than 1. The mean age of patients in this study was 40.5 years, the mean disease duration was 6.5 years, and the mean baseline Mayo score (prior to the start of the induction phase) was 8.6 points.

The rate of clinical response at Week 6 was significantly higher in the vedolizumab arm compared to the placebo arm (47.1% vs 25.5%; *P*<.0001). Vedolizumab also showed significantly higher rates of clinical remission at Week 6 (16.9% for vedolizumab vs 5.4% for placebo; *P*=.0010) and mucosal healing at Week 6 (40.9% for vedolizumab vs 24.8% for placebo, *P*=.0013). Interestingly, the magnitude of improvement in clinical response was more profound among patients without prior anti–TNF-α exposure (26.8% improvement with vedolizumab vs placebo) compared to patients who had previously been exposed to anti–TNF-α agents (18.4% improvement with vedolizumab vs placebo). The same observation was found regarding the magnitude of improvement in clinical remission: 16.5% improvement for vedolizumab versus placebo in anti–TNF-α–naïve patients compared to 6.6% improvement for vedolizumab versus placebo in anti–TNF-α–experienced patients. Finally, preliminary analyses of the safety data through Week 6 showed similar rates of adverse events, serious adverse events, and serious infections for the vedolizumab group and the placebo group.

In conclusion, this trial demonstrated that vedolizumab is significantly more effective than placebo for induction of clinical response, clinical remission, and mucosal healing in patients with moderately to severely active UC, including patients who were previously exposed to anti–TNF-α therapy and those naïve to anti–TNF-α therapy.

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Novel Infliximab and Antibody-to-Infliximab Assays Are Predictive of Disease Activity in Patients with Crohn's Disease

Several theories have been proposed to explain why Crohn's disease (CD) patients lose response to infliximab; low trough infliximab levels and the development of antibodies to infliximab (ATIs) are 2 of the most widely such studied hypotheses. In 1 study of infliximab-treated CD patients, those with a loss of response had significantly lower infliximab trough levels (median, 0 µg/mL) and significantly higher ATI levels (median, 35 U/mL) compared to patients who maintained response (median infliximab level, 2.8 µg/mL; median ATI level, 0 U/mL; *P*<.0001 for both comparisons).[1] A separate study of 105 CD patients showed that ATIs were detectable in 21% of patients after a median of 14 infusions. Further, the rate of clinical remission with infliximab treatment was higher among individuals with detectable versus undetectable trough serum infliximab levels (82% vs 6%; *P*<.001). Detectable trough serum infliximab levels were also significantly associated with lower C-reactive protein (CRP) levels (2 µg/L vs 11.8 µg/L; *P*<.001).[2] Thus, monitoring both infliximab trough levels and ATI levels may help to guide infliximab dose adjustment and clinical decision-making in order to optimize patient outcomes.

Several methods are available to measure infliximab trough and ATI levels. These methods include solid-phase enzyme-linked immunosorbent assay (ELISA), bridging ELISA, and radioimmunoassay. However, the utility of these assays is limited by their inability to accurately measure ATI levels in the presence of infliximab. At the 2012 Digestive Disease Week (DDW) meeting held May 19–22, 2012 in San Diego, California, Severine Vermeire presented results showing that a novel homogeneous mobility shift assay can measure both ATI levels and infliximab trough levels without interference between the drug and the antibody.[3]

This assay uses a fluorescently labeled version of infliximab, which is incubated in serum from an infliximab-treated CD patient. During this incubation period, the labeled infliximab complexes with any ATIs present in the sample. Following equilibration, both the labeled infliximab and the ATI-bound labeled infliximab complex are resolved by size exclusion high performance liquid chromatography (HPLC), with the latter complex displaying a later peak due to its larger size. The ratio of these 2 unique peaks results in the mobility shift.

This mobility shift assay was used to evaluate the association between inf-

ABSTRACT SUMMARY New Assay to Detect Infliximab Levels and Anti-Infliximab Antibodies From a Single Serum Sample Is Useful in Measuring Efficacy of Treatment with Infliximab in Children with IBD

The most widespread method for detection of ATIs is a double-antigen ELISA, which uses infliximab as both the ligand and the detection antibody. However, this assay is limited by its inability to accurately determine ATI levels in the presence of serum infliximab concentrations. In a poster presented at the 2012 DDW meeting, Gabor Veres and colleagues reported on the development of a novel homogeneous mobility shift assay and demonstrated that it could detect both infliximab and ATIs in the same serum sample.[1]

The homogeneous mobility shift assay uses fluorescently labeled infliximab, which has a molecular weight of approximately 150 kD. This labeled infliximab is incubated in serum from infliximab-treated patients, and the labeled infliximab forms complexes with any ATIs that may be present in the sample. The large fluorescently labeled infliximab-ATI complex has a distinct peak when subjected to HPLC. Similarly, fluorescently labeled tumor necrosis factor α (TNF-α) is also added to infliximab-treated serum; after incubation, this labeled TNF-α will be bound to any infliximab present in the sample. Again, the resulting immunocomplex has a high molecular weight and a distinctive peak by HPLC.

This novel homogeneous mobility shift assay was used to measure serum infliximab concentrations and ATI levels in 230 serum samples from 71 pediatric inflammatory bowel disease (IBD) patients. A subset of these children (n=31) also had 6 serial trough infliximab measurements, each taken prior to an infusion. A 5 mg/kg induction dose of infliximab was administered at Weeks 0, 2, and 6, followed by maintenance dosing every 8 weeks.

ATIs were detected in 20.4% of the serum samples (range, 0.28–800+ U/mL) and in 29.6% of the 71 children. Of the 47 ATI-positive serum samples, 8 also demonstrated measurable infliximab serum concentrations (range, 0.77–19.27 μg/mL). In the subset of children with serial trough level measurements, 8 had ATI-positive serum samples. Among ATI-positive samples, the median infliximab serum concentration was 0 μg/mL; in contrast, the median infliximab serum concentration among ATI-negative samples was 2.55 μg/mL ($P<.0001$). None of the ATI-positive samples exhibited infliximab serum concentrations of 3 μg/mL or higher, while 45% of the ATI-negative samples had infliximab levels of 3 μg/mL or higher. ATI-positive patients also had CRP levels that were approximately 1.5-fold higher than CRP levels in ATI-negative patients. A linear regression model found that a majority (88%) of children in the subset of patients with serum infliximab concentrations of 3 μg/mL or higher showed a decrease in CRP levels.

In conclusion, the investigators showed that ATI positivity may be a predictor of lower infliximab levels and increased CRP levels in pediatric IBD patients. As expected, higher infliximab levels (≥3 μg/mL) correlated with lower CRP levels. Importantly, this novel homogeneous mobility shift assay allowed simultaneous detection of serum infliximab concentrations as well as ATIs.

Reference

1. Veres G, Kaplan JL, De Greef E, et al. New assay to detect infliximab levels and anti-infliximab antibodies from a single serum sample is useful in measuring efficacy of treatment with infliximab in children with IBD. Presented at Digestive Disease Week; May 19–22, 2012; San Diego, California. Abstract Sa2037.

liximab trough levels, ATI levels, and disease activity (as assessed by CRP levels) in infliximab-treated CD patients. A total of 1,487 serum samples from 483 CD patients were analyzed; all patients had received maintenance infliximab therapy during 1 of 4 studies: (1) the COMMIT trial, a randomized controlled trial designed to evaluate the effect of an immunomodulator on maintenance infliximab therapy; (2) a cross-sectional Canadian study that investigated the loss of response to infliximab; (3) a cohort trial that assessed the effect of infliximab dosing on ATIs; and (4) a second cohort trial that studied the withdrawal of concomitant immunomodulator therapy in patients treated with infliximab and an immunomodulator. All serum samples were obtained while the patients were on maintenance treatment. Approximately two thirds (64%) of patients had infliximab trough levels of 3 μg/mL or higher, and nearly one quarter (24%) of patients were ATI-positive. Because patients were on maintenance infliximab treatment, their disease was relatively well controlled; the median CRP level was 3.56 μg/L.

Using the mobility shift assay, both infliximab trough levels and ATI levels were measured. The majority of samples (72%) had high infliximab trough levels and no detectable ATIs. In contrast, only a small minority of samples (3.7%) had undetectable trough infliximab levels and no detectable ATIs. The remaining patients either had undetectable trough levels and detectable levels of ATIs (13.4%), or they had detectable infliximab trough levels and detectable ATI levels (10%). These data were used to construct a receiver operating characteristic (ROC) curve, which showed that an infliximab cutoff of 3 μg/mL could accurately predict CD activity as measured by CRP level.

Among ATI-negative patients, the median CRP level was significantly lower in those individuals who had high infliximab trough levels. However, this inverse correlation was

ABSTRACT SUMMARY Association of Serum Infliximab and Antibodies to Infliximab to Long-Term Clinical Outcome in Acute Ulcerative Colitis

In a poster presented at the 2012 DDW meeting, Sanjay Murthy and colleagues used a newly developed homogeneous mobility shift assay to assess the relationships among trough infliximab levels, ATI levels, and long-term clinical outcomes in patients with acute UC.[1] A total of 134 patients with corticosteroid-refractory acute UC were included in this analysis; 103 patients had pancolitis, and 31 patients had disease limited to the splenic fixture. All patients had received 5 mg/kg infliximab induction therapy on Weeks 0, 2, and 6, followed by scheduled maintenance therapy. Corticosteroid-free remission (defined as a Mayo clinic score of 0) and colectomy were used as endpoints in this evaluation. At baseline, the median Mayo clinic score was 9 points (range, 6–12 points).

After a median follow-up period of 19.9 months (IQR, 7.6–47.4 months), 43.3% of patients were in corticosteroid-free remission, and 39.6% had undergone colectomy. The median time to colectomy was 6.5 months (IQR, 2.3–13.4 months). Among 125 patients with evaluable serum samples, 54.4% (n=68) had detectable trough levels of serum infliximab. Of these 68 patients, 6 patients (8.8%) also had detectable levels of ATIs. Of the 57 patients (45.6%) who had undetectable trough serum infliximab levels, 45 patients (78.9%) were ATI-positive, and 12 patients (21.1%) were ATI-negative.

Importantly, the investigators showed that a trough infliximab level above 2 µg/mL was associated with a higher rate of corticosteroid-free remission compared to a trough infliximab level of 2 µg/mL or lower (69% vs 16%; *P*<.001). This relationship was sustained throughout the follow-up period. In contrast, a trough infliximab level below 2 µg/mL was significantly associated with an increased risk for colectomy compared to a trough infliximab level above 2 µg/mL (64% vs 13%; *P*<.001).

Reference

1. Murthy S, Kevans D, Seow CH, et al. Association of serum infliximab and antibodies to infliximab to long-term clinical outcome in acute ulcerative colitis. Presented at Digestive Disease Week; May 19–22, 2012; San Diego, California. Abstract Sa2047.

lost among ATI-positive patients, who showed high median CRP levels regardless of infliximab trough level. Multivariate analysis confirmed that both infliximab trough level and ATI status could independently predict CRP level. Infliximab trough levels negatively correlated with CRP levels, with the median CRP level being 52% lower in patients with an infliximab trough level of 3 µg/mL or higher compared to patients with an infliximab trough level below 3 µg/mL. ATI levels also correlated with CRP: In patients with an infliximab trough level below 3 µg/mL, the median CRP level was higher among ATI-positive patients compared to ATI-negative patients (8.4 µg/L vs 5.65 µg/L, respectively; *P*<.001). The same trend was observed in patients with an infliximab trough level of 3 µg/mL or higher (9.9 µg/L for ATI-positive patients vs 1.5 µg/L for ATI-negative patients; *P*<.01).

Based on these results, the investigators concluded that this novel homogeneous mobility shift assay could accurately measure both infliximab trough levels and ATI levels without the interference that limits other currently used assays. Using the homogeneous mobility shift assay, they confirmed that CRP levels were strongly associated with infliximab trough levels. Further, this study was the first to demonstrate that CRP levels were higher among ATI-positive patients versus ATI-negative patients independent of infliximab trough levels; this finding contradicts the previously held theory that ATI positivity would not predict high CRP levels as long as infliximab trough levels remained sufficiently high. Further study is required to determine the best strategy for management of patients who lose response to infliximab and/or develop ATIs in the setting of sufficiently high trough infliximab levels.

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2. Maser EA, Villela R, Silverberg MS, Greenberg GR. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. *Clin Gastroenterol Hepatol.* 2006;4:1248-1254.

3. Feagan BG, Singh S, Lockton S, et al. Novel infliximab (IFX) and antibody-to-infliximab (ATI) assays are predictive of disease activity in patients with Crohn's disease (CD). Presented at Digestive Disease Week; May 19–22, 2012; San Diego, California. Abstract 565.

Accelerated Step-Care Therapy with Early Azathioprine Versus Conventional Step-Care Therapy in Crohn's Disease: A Randomized Study

Three main strategies have been widely proposed to treat CD: (1) conventional step-up therapy, (2) an early top-down strategy, and (3) an accelerated step-up strategy. In the third paradigm, immunosuppressive agents (particularly azathioprine) are prescribed concomitantly with the first course of corticosteroids.

The strongest evidence supporting the accelerated step-up strategy is provided by a study from Markowitz and colleagues.[1] In this prospective, double-blind, placebo-controlled trial, pediatric patients who received 6-mercaptopurine had a shorter duration of corticosteroid use compared to patients who received placebo (observed-to-expected ratio, 0.73 days with prednisone vs 1.34 days with prednisone; $P<.001$). Additionally, while the rate of remission was similar with both treatment strategies (89% in both groups), the rate of relapse after remission was much lower in the 6-mercaptopurine–treated group compared to the placebo group (9% vs 47%; $P=.007$).

However, these results were not recapitulated in the Spanish AZTEC trial, which assessed early use of azathioprine versus placebo in adults who had been recently diagnosed with CD.[2] There was no significant difference in this study's primary endpoint of sustained clinical remission (defined as a CDAI score <150 points at 18 months) between patients treated with azathioprine and those who received placebo (67.7% vs 57.1%; $P=.2$). Further, a nonresponder imputation analysis (in which missing scores were considered as treatment failures) showed even lower rates of sustained remission for both the azathioprine and placebo groups (44.1% vs 38.1%, respectively; $P=.5$). However, one benefit of early azathioprine therapy was an associated reduction in the cumulative dose of corticosteroids compared to the placebo group.

ABSTRACT SUMMARY One Third of Patients Treated with Adalimumab or Infliximab for Crohn's Disease or Ulcerative Colitis Permanently Dose Escalate Due to Loss of Response

Despite the significant efficacy of infliximab and adalimumab for the treatment of IBD, many patients lose response to these drugs. In a poster presented at the 2012 DDW meeting, Darryl Fedorak and colleagues reported the findings of a retrospective chart review in which they sought to determine the incidence of loss of response among patients treated with either of these 2 agents.[1] They further evaluated these charts to determine how many patients required dose escalation.

The investigators identified 363 patients who met the inclusion criteria for this study. All enrolled patients had an initial response to induction dosing with either infliximab (5 mg/kg administered at Weeks 0, 2, and 6) or adalimumab (160 mg and 80 mg administered at Weeks 0 and 2, respectively). Patients also had to have advanced to scheduled maintenance therapy (every 8 weeks with infliximab or every 2 weeks with adalimumab), achieved a stable corticosteroid-free clinical benefit that was durable for a minimum of 6 months, and exhibited a loss of response to their anti–TNF-α therapy. Finally, enrolled patients had to have sufficient follow-up to allow assessment of ongoing wellness and/or disease relapse with dose-escalated treatment.

At the time of the analysis, 65% of infliximab-treated patients remained in remission while on infliximab maintenance therapy at a dose of 5 mg/kg infliximab every 8 weeks. Similarly, 72% of adalimumab-treated patients were in remission on maintenance therapy with 40 mg adalimumab every other week. Thirty-five percent of patients who received infliximab required dose escalation (to 5 mg/kg every 4 weeks). Twenty-eight percent of adalimumab-treated patients required dose escalation (to 40 mg weekly). There was no significant difference in the rates of dose escalation between ulcerative colitis (UC) and CD patients. Further, a Kaplan-Meier plot found no significant difference in the time to treatment failure between infliximab and adalimumab (Log-rank $P=.56$). Finally, dose de-escalation was uncommon. Only 7 infliximab-treated patients underwent dose de-escalation to the original doses; none of the adalimumab-treated patients underwent dose de-escalation.

Reference

1. Fedorak DK, Osatiuk P, Wong K, et al. One third of patients treated with adalimumab or infliximab for Crohn's disease or ulcerative colitis permanently dose escalate due to loss of response. Presented at Digestive Disease Week; May 19–22, 2012; San Diego, California. Abstract Sa2049.

Given these findings, Jacques Cosnes and colleagues conducted a multicenter, open-label, randomized study to compare an azathioprine-based, accelerated step-up strategy with conventional step-up therapy in patients with early CD. Results of this trial were presented at the 2012 DDW meeting.[3]

All patients were recruited from multiple centers throughout France and Belgium. Patients enrolled in this study were at least 18 years of age at diagnosis, had been diagnosed with CD less than 6 months prior to enrollment, had not been previously treated with immunosuppressants, and had not previously undergone surgery. Additionally, patients were required to meet at least 2 of the following conditions, which predicted a high-risk for the development of disabling disease: requirement of corticosteroids at first disease flare, age less than 40 years, and perianal disease.

Enrolled patients were randomized to either conventional step-up management or accelerated step-up management; in the latter group, the starting azathioprine dose was 2.5 mg/kg. The primary study endpoint was remission rate, which was strictly defined as no active disease, no requirement for corticosteroids, no treatment with anti–TNF-α therapy, no hospitalization-induced disease, no symptomatic perianal lesions, and no abdominal or perianal surgery.

A total of 147 patients were randomized to treatment. Five patients withdrew consent. Of the remaining 142 patients, 66 patients in the accelerated step-up arm and 68 patients in the conventional step-up arm were evaluable with at least 3 months of follow-up. At baseline, patients did not have active disease and demonstrated normal hemoglobin levels and normal or slightly elevated CRP levels.

The median proportion of patients who achieved remission was very similar between the 2 treatment groups. The accelerated step-up arm showed a trend toward a higher median remission rate during the first year of therapy, but this difference did not reach statistical significance and was not maintained over the course of follow-up. Likewise, there were no differences between arms in terms of median CDAI scores, serum CRP levels, or the median time to first introduction of anti–TNF-α therapy or first abdominal surgery. Overall, this study showed that an accelerated, azathioprine-based, step-up strategy was not associated with improvement in CD remission rates compared to a conventional step-up treatment strategy.

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3. Cosnes J, Bourrier A, Laharie D, et al. Accelerated step-care therapy with early azathioprine (AZA) vs. conventional step-care therapy in Crohn's disease. A randomized study. Presentation at Digestive Disease Week; May 19–22, 2012; San Diego, California. Abstract 943c.

PIANO: A 1,000-Patient Prospective Registry of Pregnancy Outcomes in Women with IBD Exposed to Immunomodulators and Biologic Therapy

Many women with IBD are of childbearing age, and previous studies have shown that these women have increased risks of adverse pregnancy outcomes and labor and/or delivery complications compared to the general population. Whenever possible, IBD medications are continued during pregnancy in order to achieve or maintain remission, but the safety of immunomodulator and/or biologic therapy during pregnancy has not been comprehensively studied.

At the 2012 DDW meeting, Uma Mahadevan summarized results from a study designed to more accurately determine the safety of immunomodulator and biologic therapy during pregnancy.[1] This study enrolled a large prospective cohort of pregnant women with IBD (N=1,115) who were identified from 30 member sites of the Crohn's and Colitis Foundation of America; 57% of these patients had CD, and 40% had UC. Data were collected by telephone or through an in-person questionnaire at several time points: at intake, during each trimester of pregnancy, at delivery, and every 4 months during the first year of the child's life. The mother's medical history was also recorded, including medication exposure, IBD duration, and disease activity and complications during pregnancy and the postpartum period. Pregnancy outcomes, maternal disease course, newborn complications, and growth and developmental milestones were recorded for the first year after birth.

Patients were divided into 4 categories based on their drug exposure between conception and delivery: (1) unexposed patients (N=306)

who did not receive immunomodulator or biologic therapy during the study but were instead treated with mesalamine, corticosteroids, or antibiotics; (2) immunomodulator-treated patients (N=204) who received either azathioprine or 6-mercaptopurine; (3) anti–TNF-α–treated patients (N=291) who received either infliximab, adalimumab, certolizumab pegol, or natalizumab during the study; or (4) combination-treated patients (N=75) who received both immunomodulators and anti–TNF-α agents during the study. At the time of the 2012 DDW presentation, 896 women had completed their pregnancies.

The demographics of the mothers differed across treatment groups. More CD patients had been exposed to biologic therapy (43%) compared to UC patients. Among UC patients, 65–75% had inactive disease during pregnancy, and fewer patients had inactive disease at the beginning of pregnancy than 12 months postpartum. In contrast, more CD patients had inactive disease during pregnancy (80–90%), and these patients were more likely to have inactive disease at the beginning of pregnancy than postpartum.

After adjusting for the effects of the underlying disease, most adverse incidents—including spontaneous abortions or congenital anomalies—did not occur at a significantly increased rate among women enrolled in this study compared to community-based or national rates. However, there were a few exceptions: Women in this study had a higher rate of Caesarean sections, and their babies had a higher rate of neonatal intensive care unit stay. Also, there were higher rates of spontaneous abortions and Cesarean sections in the anti–TNF-α group, and there was a higher rate of preterm births among women in the combination therapy group.

While babies of mothers with CD showed no increase in any complications or adverse effects, a nearly 5-fold higher rate of spontaneous abortion was observed among mothers with UC who were treated with anti–TNF-α agents. Further, UC mothers in the combination therapy group had an increased risk of any complication—including preterm birth, low birth weight, and neonatal intensive care unit stay—after the analysis adjusted for disease activity.

There were no significant differences in the growth characteristics of the babies throughout their first year, including height, weight, and developmental measurements at 4, 9, and 12 months of age (adjusted for maternal age and disease activity). In addition, no association was found between congenital anomalies and drug exposure. Finally, the rate of infections among the infants was not significantly affected by drug exposure; however, when certolizumab pegol was removed from the analysis, the rate of infections in babies at 1 year of age was higher among babies whose mothers were in the combination therapy group (relative risk, 1.38). Taken together, these results suggest that the mother's disease may confer a higher risk to the fetus than the risks associated with the use of immunomodulator or biologic therapy.

Reference

1. Mahadevan U, Martin CF, Sandler RS, et al. PIANO: a 1000 patient prospective registry of pregnancy outcomes in women with IBD exposed to immunomodulators and biologic therapy. Presented at Digestive Disease Week; May 19–22, 2012; San Diego, California. Abstract 865.

Commentary

William J. Sandborn, MD

The 2012 DDW meeting—which was held May 19–22, 2012 in San Diego, California—included a number of important studies, several of which are summarized in this supplement. While all of this data is relevant and worthy of consideration, the 3 studies I feel are most noteworthy are highlighted below.

First, the presentation on azathioprine by Jacques Cosnes suggests that this drug may be less effective than was previously thought.[1] Azathioprine has been used to treat CD in a few centers since the early 1980s and worldwide since the early 1990s, but the FDA has never approved azathioprine as a treatment for CD. In large part, this lack of approval stems from the fact that azathioprine has been available as a generic drug since the late 1990s, so pharmaceutical companies have had little incentive to perform the large clinical trials needed to definitively demonstrate azathioprine's safety and efficacy for the treatment of CD. In the absence of large clinical trials, clinicians have based their use of azathioprine on smaller, investigator-initiated trials, which has led to some challenges. Specifically, we lack data to show that the clinical benefits of azathioprine monotherapy outweigh its risks—which include nonmelanoma skin cancer and non-Hodgkin lymphoma, according to recent studies.

The French study presented by Cosnes helps to answer this question by testing whether early and more extensive use of azathioprine in patients with CD is effective. When prescribing anti–TNF-α drugs, many clinicians use a "top-down" treatment strategy, in which anti–TNF-α therapy is initiated early in the course of CD in an effort to improve clinical outcomes and potentially change the natural history of the disease. The study presented by Cosnes aimed to test whether the same goal could be achieved with early use of azathioprine combined with a tapering course of prednisone. Early azathioprine treatment was compared to a traditional "step-up" treatment strategy, in which clinicians started with less effective therapies, then advanced to prednisone, and finally added azathioprine, if it was needed.

While studies have demonstrated that early use of anti–TNF-α therapy leads to better clinical outcomes, the data presented by Cosnes showed that early use of azathioprine was not more effective than the classical step-up treatment strategy. This finding confirmed that of a similar study presented by Miquel Sans at the 2011 DDW meeting, which achieved essentially the same result.[2] Thus, 2 randomized trials in adults have shown that early use of azathioprine does not improve clinical outcomes and does not change the course of CD when compared to later use of azathioprine (or, in the case of the Sans trial, to placebo).

Given that other trials have shown some degree of benefit with azathioprine, I think it is probably incorrect to conclude that azathioprine has no efficacy. However, these 2 trials show that the magnitude of efficacy with azathioprine is considerably less than was previously believed. When these data are considered alongside emerging data about the toxicity of azathioprine—which suggest that the side effects of this drug are greater than was initially thought—the totality of the benefit versus risk of azathioprine monotherapy certainly appears less favorable now than it did 5–10 years ago. In contrast, the SONIC trial clearly showed that azathioprine combined with anti–TNF-α therapy was more effective than monotherapy with either drug alone.[3] Thus, clinicians may want to reconsider how they use azathioprine in clinical practice, changing from azathioprine monotherapy to combination therapy with azathioprine plus an anti–TNF-α drug.

The second DDW presentation that deserves special mention is the GEMINI trial, which studied vedolizumab for the treatment of UC. In a 2005 paper published in *The New England Journal of Medicine*, Brian Feagan and coauthors presented data from a phase II study that demonstrated the efficacy of vedolizumab in patients with UC who were failing first-line therapy with mesalamine.[4] This study was the first positive study to show that blocking lymphocyte trafficking to the gut could effectively treat UC; however, it did not assess vedolizumab as maintenance therapy, and it did not include treatment-refractory patients. The GEMINI trial was conducted to address these gaps.

In a presentation at the 2012 DDW meeting, Feagan definitively showed that vedolizumab is effective for inducing response, remission, and mucosal healing in a cohort of outpatients with severe UC, approximately half of whom were failing anti–TNF-α therapy.[5] Data on the use of vedolizumab for maintenance therapy will be presented at the American College of Gastroenterology (ACG) meeting later this year.

One major benefit of vedolizumab is its apparent specificity for the gut, which will hopefully prevent some of the side effects that have been associated with natalizumab. Because natalizumab blocks lymphocyte trafficking

in the brain as well as in the gut, this drug can reduce immune surveillance in the brain, which puts patients at risk for progressive multifocal leukoencephalopathy (PML). This risk has precluded the widespread use of natalizumab for the treatment of CD. Because vedolizumab is gut-specific, however, it blocks lymphocyte trafficking and prevents inflammation in the gut without increasing the risk for PML. Overall, the vedolizumab data presented at DDW suggest that this drug is effective for the treatment of UC, even in patients who have failed prior anti–TNF-α therapy—a difficult-to-treat group that is frequently encountered in clinical practice. Hopefully, vedolizumab will be approved for clinical use within the next 1–2 years.

Finally, the golimumab data from the PURSUIT-SC trial also deserves careful consideration.[6] Currently, 3 anti–TNF-α drugs are approved in the United States for the treatment of CD: infliximab, adalimumab, and certolizumab pegol. However, only infliximab is approved for the treatment of UC, which limits clinicians' ability to provide optimal patient care. In an effort to give clinicians more treatment options for UC, the new drug golimumab was recently evaluated in a phase II/III induction study, results of which were presented during the 2012 DDW meeting.

This trial demonstrated that golimumab is effective for inducing response, remission, and mucosal healing in a cohort of outpatients with moderate-to-severe UC who were naïve to anti–TNF-α therapy. Data from the maintenance phase of this study will likely be presented at the ACG meeting later this year. The data from the PURSUIT-SC study should be sufficient to support regulatory review of golimumab, and this drug will likely be approved within the next 1–2 years.

In addition to this data on golimumab, the FDA is also currently reviewing data that supports the use of adalimumab as a treatment for UC, and I am hopeful that both drugs will receive FDA approval for the treatment of UC in the near future. At that point, a range of anti–TNF-α drugs will be available for the treatment of UC—including some drugs that can be administered subcutaneously—which would give clinicians the same degree of flexibility when treating UC that they currently enjoy when treating CD.

In conclusion, I think both Cosnes' study of azathioprine and the PURSUIT-SC trial have immediate relevance to clinical practice, as both studies provide data that could be helpful when clinicians are deciding on therapy for specific patients. As clinical practice evolves, we may need to consider a reappraisal of some of the drugs currently in use, like azathioprine, and we will also need to make room for a variety of new treatment options—both new members of existing classes of drugs, like golimumab, and new drugs in entirely new classes, like vedolizumab.

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REMICADE (infliximab)
Lyophilized Concentrate for Injection, for Intravenous Use
Brief Summary of Full Prescribing Information

WARNING: SERIOUS INFECTIONS and MALIGNANCY

SERIOUS INFECTIONS

Patients treated with REMICADE® are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions and Adverse Reactions]* Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

REMICADE should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before REMICADE use and during therapy.[1,2] Treatment for latent infection should be initiated prior to REMICADE use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

The risks and benefits of treatment with REMICADE should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with REMICADE, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including REMICADE *[see Warnings and Precautions]*.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including REMICADE. These cases have had a very aggressive disease course and have been fatal. All reported REMICADE cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. All of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with REMICADE at or prior to diagnosis.

CONTRAINDICATIONS: REMICADE at doses >5 mg/kg should not be administered to patients with moderate to severe heart failure. In a randomized study evaluating REMICADE in patients with moderate to severe heart failure (New York Heart Association [NYHA] Functional Class III/IV), REMICADE treatment at 10 mg/kg was associated with an increased incidence of death and hospitalization due to worsening heart failure *[see Warnings and Precautions and Adverse Reactions]*. REMICADE should not be re-administered to patients who have experienced a severe hypersensitivity reaction to REMICADE. Additionally, REMICADE should not be administered to patients with known hypersensitivity to inactive components of the product or to any murine proteins. **WARNINGS AND PRECAUTIONS: Serious Infections:** Patients treated with REMICADE are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic organisms including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF-blockers. Patients have frequently presented with disseminated rather than localized disease. Treatment with REMICADE should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants such as corticosteroids or methotrexate may be at greater risk of infection. The risks and benefits of treatment should be considered prior to initiating therapy in patients: • with chronic or recurrent infection; • who have been exposed to tuberculosis; • with a history of an opportunistic infection • who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or • with underlying conditions that may predispose them to infection. ***Tuberculosis:*** Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving REMICADE, including patients who have previously received treatment for latent or active tuberculosis. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating REMICADE and periodically during therapy. Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been

shown to reduce the risk of tuberculosis reactivation during therapy. Induration of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis is needed prior to initiating REMICADE, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG). Anti-tuberculosis therapy should also be considered prior to initiation of REMICADE in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient. Tuberculosis should be strongly considered in patients who develop a new infection during REMICADE treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis. ***Monitoring:*** Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with REMICADE, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with REMICADE. REMICADE should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with REMICADE should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated. ***Invasive Fungal Infections:*** For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy. **Malignancies:** Malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤ 18 years of age), including REMICADE. Approximately half of these cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months (range 1 to 84 months) after the first dose of TNF blocker therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources, including registries and spontaneous postmarketing reports. ***Lymphomas:*** In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. In the controlled and open-label portions of REMICADE clinical trials, 5 patients developed lymphomas among 5707 patients treated with REMICADE (median duration of follow-up 1.0 years) vs. 0 lymphomas in 1600 control patients (median duration of follow-up 0.4 years). In rheumatoid arthritis patients, 2 lymphomas were observed for a rate of 0.08 cases per 100 patient-years of follow-up, which is approximately three-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 5 lymphomas were observed for a rate of 0.10 cases per 100 patient-years of follow-up, which is approximately four-fold higher than expected in the general population. Patients with Crohn's disease, rheumatoid arthritis or plaque psoriasis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy. Cases of acute and chronic leukemia have been reported with postmarketing TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia. ***Hepatosplenic T-cell lymphoma (HSTCL):*** Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including REMICADE. These cases have had a very aggressive disease course and have been fatal. All reported REMICADE cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. All of these patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine concomitantly with REMICADE at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to REMICADE or REMICADE in combination with these other immunosuppressants.When treating patients with inflammatory bowel disease, particularly in adolescents and young adults, consideration of whether to use REMICADE alone or in combination with other immunosuppressants should take into account a possibility that there is a higher risk of HSTCL with combination therapy versus an observed increased risk of immunogenicity and hypersensitivity reactions with REMICADE monotherapy from the clinical trial data *[see Warnings and Precautions and Adverse Reactions]*. ***Other Malignancies:*** In the controlled portions of clinical trials of some TNF-blocking agents including REMICADE, more malignancies (excluding lymphoma and nonmelanoma skin cancer [NMSC]) have been observed in patients receiving

REMICADE® (infliximab)

those TNF-blockers compared with control patients. During the controlled portions of REMICADE trials in patients with moderately to severely active rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 14 patients were diagnosed with malignancies (excluding lymphoma and NMSC) among 4019 REMICADE-treated patients vs. 1 among 1597 control patients (at a rate of 0.52/100 patient-years among REMICADE-treated patients vs. a rate of 0.11/100 patient-years among control patients), with median duration of follow-up 0.5 years for REMICADE-treated patients and 0.4 years for control patients. Of these, the most common malignancies were breast, colorectal, and melanoma. The rate of malignancies among REMICADE-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected. In a clinical trial exploring the use of REMICADE in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, the majority of lung or head and neck origin, were reported in REMICADE-treated patients compared with control patients. All patients had a history of heavy smoking *[see Adverse Reactions]*. Prescribers should exercise caution when considering the use of REMICADE in patients with moderate to severe COPD. Psoriasis patients should be monitored for nonmelanoma skin cancers (NMSCs), particularly those patients who have had prior prolonged phototherapy treatment. In the maintenance portion of clinical trials for REMICADE, NMSCs were more common in patients with previous phototherapy *[see Adverse Reactions]*. The potential role of TNF-blocking therapy in the development of malignancies is not known *[see Adverse Reactions]*. Rates in clinical trials for REMICADE cannot be compared to rates in clinical trials of other TNF-blockers and may not predict rates observed in a broader patient population. Caution should be exercised in considering REMICADE treatment in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving REMICADE. **Hepatitis B Virus Reactivation:** Use of TNF blockers, including REMICADE, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients should be tested for HBV infection before initiating TNF blocker therapy, including REMICADE. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, TNF blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, prescribers should exercise caution when considering resumption of TNF blocker therapy in this situation and monitor patients closely. **Hepatotoxicity:** Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis, have been reported rarely in postmarketing data in patients receiving REMICADE. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between 2 weeks to more than 1 year after initiation of REMICADE; elevations in hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver transplantation. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g., $\geq$5 times the upper limit of normal) develop, REMICADE should be discontinued, and a thorough investigation of the abnormality should be undertaken. In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving REMICADE without progression to severe hepatic injury *[see Adverse Reactions]*. **Patients with Heart Failure:** REMICADE has been associated with adverse outcomes in patients with heart failure, and should be used in patients with heart failure only after consideration of other treatment options. The results of a randomized study evaluating the use of REMICADE in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg REMICADE, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking REMICADE. There have also been rare post-marketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a decision is made to administer REMICADE to patients with heart failure, they should be closely monitored during therapy, and REMICADE should be discontinued if new or worsening symptoms of heart failure appear *[see Contraindications and Adverse Reactions]*. **Hematologic Reactions:** Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving REMICADE. The causal relationship to REMICADE therapy remains unclear. Although no high-risk group(s) has been identified, caution should be exercised in patients being treated with REMICADE who have ongoing or a history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever) while on REMICADE. Discontinuation of REMICADE therapy should be considered in patients who develop significant hematologic abnormalities. **Hypersensitivity:** REMICADE has been associated with hypersensitivity reactions that vary in their time of onset and required hospitalization in some cases. Most hypersensitivity reactions, which include urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of REMICADE infusion. However, in some cases, serum sickness-like reactions have been observed in patients after initial REMICADE therapy (i.e., as early as after the second dose), and when REMICADE therapy was reinstituted following an extended period without REMICADE treatment. Symptoms associated with these reactions include 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, loss of detectable serum concentrations of infliximab, and possible loss of drug efficacy. REMICADE should be discontinued for severe hypersensitivity reactions. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be available for immediate use in the event of a reaction *[see Adverse Reactions]*. In rheumatoid arthritis, Crohn's disease and psoriasis clinical trials, re-administration of REMICADE after a period of no treatment resulted in a higher incidence of infusion reactions relative to regular maintenance treatment *[see Adverse Reactions]*. In general, the benefit-risk of re-administration of REMICADE after a period of no-treatment, especially as a re-induction regimen given at weeks 0, 2 and 6, should be carefully considered. In the case where REMICADE maintenance therapy for psoriasis is interrupted, REMICADE should be reinitiated as a single dose followed by maintenance therapy. **Neurologic Reactions:** REMICADE and other agents that inhibit TNF have been associated in rare cases with CNS manifestation of systemic vasculitis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and optic neuritis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of REMICADE in patients with these neurologic disorders and should consider discontinuation of REMICADE if these disorders develop. **Use with Anakinra:** Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and another TNFα-blocking agent, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse reactions seen with the combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNFα-blocking agents. Therefore, the combination of REMICADE and anakinra is not recommended. **Use with Abatacept:** In clinical studies, concurrent administration of TNF-blocking agents and abatacept have been associated with an increased risk of infections including serious infections compared with TNF-blocking agents alone, without increased clinical benefit. Therefore, the combination of REMICADE and abatacept is not recommended *[see Drug Interactions]*. **Switching between Biological Disease-Modifying Antirheumatic Drugs (DMARDs):** Care should be taken when switching from one biologic to another, since overlapping biological activity may further increase the risk of infection. **Autoimmunity:** Treatment with REMICADE may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with REMICADE, treatment should be discontinued *[see Adverse Reactions]*. **Vaccinations:** No data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines in patients receiving anti-TNF therapy. It is recommended that live vaccines not be given concurrently. Caution is advised in the administration of live vaccines to infants born to female patients treated with REMICADE during pregnancy since REMICADE is known to cross the placenta and has been detected up to 6 months in the serum of infants born to female patients treated with REMICADE during pregnancy. It is recommended that all pediatric patients be brought up to date with all vaccinations prior to initiating REMICADE therapy. The interval between vaccination and initiation of REMICADE therapy should be in accordance with current vaccination guidelines. **ADVERSE REACTIONS: Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not predict the rates observed in broader patient populations in clinical practice. **Adverse Reactions in Adults:** The data described herein reflect exposure to REMICADE in 4779 adult patients (1304 patients with rheumatoid arthritis, 1106 patients with Crohn's disease, 202 with ankylosing spondylitis, 293 with psoriatic arthritis, 484 with ulcerative colitis, 1373 with plaque psoriasis, and 17 patients with other conditions), including 2625 patients exposed beyond 30 weeks and 374 exposed beyond 1 year. *[For information on adverse reactions in pediatric patients see Adverse Reactions.]* One of the most-common reasons for discontinuation of treatment was infusion-related reactions (e.g., dyspnea, flushing, headache and rash). ***Infusion-related Reactions:*** An infusion reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 hour after an infusion. In phase 3 clinical studies, 18% of REMICADE-treated patients experienced an infusion reaction compared to 5% of placebo-treated patients. Of infliximab-treated patients who had an infusion reaction during the induction period, 27% experienced an infusion reaction during the maintenance period. Of patients who did not have an infusion reaction during the induction period, 9% experienced an infusion reaction during the maintenance period. Among all REMICADE infusions, 3% were accompanied by nonspecific symptoms such as fever or chills, 1% were accompanied by cardiopulmonary reactions (primarily chest pain, hypotension, hypertension or dyspnea), and <1% were accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Serious infusion reactions

occurred in <1% of patients and included anaphylaxis, convulsions, erythematous rash and hypotension. Approximately 3% of patients discontinued REMICADE because of infusion reactions, and all patients recovered with treatment and/or discontinuation of the infusion. REMICADE infusions beyond the initial infusion were not associated with a higher incidence of reactions. The infusion reaction rates remained stable in psoriasis through 1 year in psoriasis Study I. In psoriasis Study II, the rates were variable over time and somewhat higher following the final infusion than after the initial infusion. Across the 3 psoriasis studies, the percent of total infusions resulting in infusion reactions (i.e., an adverse event occurring within 1 hour) was 7% in the 3 mg/kg group, 4% in the 5 mg/kg group, and 1% in the placebo group. Patients who became positive for antibodies to infliximab were more likely (approximately two- to three-fold) to have an infusion reaction than were those who were negative. Use of concomitant immunosuppressant agents appeared to reduce the frequency of both antibodies to infliximab and infusion reactions *[see Adverse Reactions and Drug Interactions]*. ***Infusion reactions following re-administration:*** In a clinical trial of patients with moderate to severe psoriasis designed to assess the efficacy of long-term maintenance therapy versus re-treatment with an induction regimen of REMICADE following disease flare, 4% (8/219) of patients in the re-treatment therapy arm experienced serious infusion reactions versus < 1% (1/222) in the maintenance therapy arm. Patients enrolled in this trial did not receive any concomitant immunosuppressant therapy. In this study, the majority of serious infusion reactions occurred during the second infusion at Week 2. Symptoms included, but were not limited to, dyspnea, urticaria, facial edema, and hypotension. In all cases, REMICADE treatment was discontinued and/or other treatment instituted with complete resolution of signs and symptoms. ***Delayed Reactions/Reactions Following Re-administration:*** In psoriasis studies, approximately 1% of REMICADE-treated patients experienced a possible delayed hypersensitivity reaction, generally reported as serum sickness or a combination of arthralgia and/or myalgia with fever and/or rash. These reactions generally occurred within 2 weeks after repeat infusion. ***Infections:*** In REMICADE clinical studies, treated infections were reported in 36% of REMICADE-treated patients (average of 51 weeks of follow-up) and in 25% of placebo-treated patients (average of 37 weeks of follow-up). The infections most frequently reported were respiratory tract infections (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. Among REMICADE-treated patients, serious infections included pneumonia, cellulitis, abscess, skin ulceration, sepsis, and bacterial infection. In clinical trials, 7 opportunistic infections were reported; 2 cases each of coccidioidomycosis (1 case was fatal) and histoplasmosis (1 case was fatal), and 1 case each of pneumocystosis, nocardiosis and cytomegalovirus. Tuberculosis was reported in 14 patients, 4 of whom died due to miliary tuberculosis. Other cases of tuberculosis, including disseminated tuberculosis, also have been reported post-marketing. Most of these cases of tuberculosis occurred within the first 2 months after initiation of therapy with REMICADE and may reflect recrudescence of latent disease *[see Warnings and Precautions]*. In the 1-year placebo-controlled studies RA I and RA II, 5.3% of patients receiving REMICADE every 8 weeks with MTX developed serious infections as compared to 3.4% of placebo patients receiving MTX. Of 924 patients receiving REMICADE, 1.7% developed pneumonia and 0.4% developed TB, when compared to 0.3% and 0.0% in the placebo arm respectively. In a shorter (22-week) placebo-controlled study of 1082 RA patients randomized to receive placebo, 3 mg/kg or 10 mg/kg REMICADE infusions at 0, 2, and 6 weeks, followed by every 8 weeks with MTX, serious infections were more frequent in the 10 mg/kg REMICADE group (5.3%) than the 3 mg/kg or placebo groups (1.7% in both). During the 54-week Crohn's II Study, 15% of patients with fistulizing Crohn's disease developed a new fistula-related abscess. In REMICADE clinical studies in patients with ulcerative colitis, infections treated with antimicrobials were reported in 27% of REMICADE-treated patients (average of 41 weeks of follow-up) and in 18% of placebo-treated patients (average 32 weeks of follow-up). The types of infections, including serious infections, reported in patients with ulcerative colitis were similar to those reported in other clinical studies. The onset of serious infections may be preceded by constitutional symptoms such as fever, chills, weight loss, and fatigue. The majority of serious infections, however, may also be preceded by signs or symptoms localized to the site of the infection. ***Autoantibodies/ Lupus-like Syndrome:*** Approximately half of REMICADE-treated patients in clinical trials who were antinuclear antibody (ANA) negative at baseline developed a positive ANA during the trial compared with approximately one-fifth of placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately one-fifth of REMICADE-treated patients compared with 0% of placebo-treated patients. Reports of lupus and lupus-like syndromes, however, remain uncommon. ***Malignancies:*** In controlled trials, more REMICADE-treated patients developed malignancies than placebo-treated patients *[see Warnings and Precautions]*. In a randomized controlled clinical trial exploring the use of REMICADE in patients with moderate to severe COPD who were either current smokers or ex-smokers, 157 patients were treated with REMICADE at doses similar to those used in rheumatoid arthritis and Crohn's disease. Of these REMICADE-treated patients, 9 developed a malignancy, including 1 lymphoma, for a rate of 7.67 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% CI 3.51 - 14.56). There was 1 reported malignancy among 77 control patients for a rate of 1.63 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% CI 0.04 - 9.10). The majority of the malignancies developed in the lung or head and neck. ***Patients with Heart Failure:*** In a randomized study evaluating REMICADE in moderate to severe heart failure (NYHA Class III/IV; left ventricular ejection fraction ≤35%), 150 patients were randomized to receive treatment with 3 infusions of REMICADE 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks. Higher incidences of mortality and hospitalization due to worsening heart failure were observed in patients receiving the 10 mg/kg REMICADE dose. At 1 year, 8 patients in the 10 mg/kg REMICADE group had died compared with 4 deaths each in the 5 mg/kg REMICADE and the placebo groups. There were trends toward increased dyspnea, hypotension, angina, and dizziness in both the 10 mg/kg and 5 mg/kg REMICADE treatment groups, versus placebo. REMICADE has not been studied in patients with mild heart failure (NYHA Class I/II) *[see Contraindications and Warnings and Precautions]*. ***Immunogenicity:*** Treatment with REMICADE can be associated with the development of antibodies to infliximab. The assay used to measure anti-infliximab antibodies in patient samples is subject to interference by serum infliximab, possibly resulting in an underestimation of the rate of patient antibody formation. The incidence of antibodies to infliximab in patients given a 3-dose induction regimen followed by maintenance dosing was approximately 10% as assessed through 1 to 2 years of REMICADE treatment. A higher incidence of antibodies to infliximab was observed in Crohn's disease patients receiving REMICADE after drug-free intervals >16 weeks. In a study of psoriatic arthritis in which 191 patients received 5 mg/kg with or without MTX, antibodies to infliximab occurred in 15% of patients. The majority of antibody-positive patients had low titers. Patients who were antibody-positive were more likely to have higher rates of clearance, reduced efficacy and to experience an infusion reaction *[see Adverse Reactions]* than were patients who were antibody negative. Antibody development was lower among rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX. In the psoriasis Study II, which included both the 5 mg/kg and 3 mg/kg doses, antibodies were observed in 36% of patients treated with 5 mg/kg every 8 weeks for 1 year, and in 51% of patients treated with 3 mg/kg every 8 weeks for 1 year. In the psoriasis Study III, which also included both the 5 mg/kg and 3 mg/kg doses, antibodies were observed in 20% of patients treated with 5 mg/kg induction (weeks 0, 2 and 6), and in 27% of patients treated with 3 mg/kg induction. Despite the increase in antibody formation, the infusion reaction rates in Studies I and II in patients treated with 5 mg/kg induction followed by every 8 week maintenance for 1 year and in Study III in patients treated with 5 mg/kg induction (14.1%-23.0%) and serious infusion reaction rates (<1%) were similar to those observed in other study populations. The clinical significance of apparent increased immunogenicity on efficacy and infusion reactions in psoriasis patients as compared to patients with other diseases treated with REMICADE over the long term is not known. The data reflect the percentage of patients whose test results were positive for antibodies to infliximab in an ELISA assay, and they are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to infliximab with the incidence of antibodies to other products may be misleading. ***Hepatotoxicity:*** Severe liver injury, including acute liver failure and autoimmune hepatitis, has been reported rarely in patients receiving REMICADE *[see Warnings and Precautions]*. Reactivation of hepatitis B virus has occurred in patients receiving TNF-blocking agents, including REMICADE, who are chronic carriers of this virus *[see Warnings and Precautions]*. In clinical trials in rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, plaque psoriasis, and psoriatic arthritis, elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving REMICADE than in controls (Table 1), both when REMICADE was given as monotherapy and when it was used in combination with other immunosuppressive agents. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of REMICADE, or modification of concomitant medications.

Table 1 Proportion of patients with elevated ALT in clinical trials

	Proportion of patients with elevated ALT					
	>1 to <3 x ULN		≥3 x ULN		≥5 x ULN	
	Placebo	REMICADE	Placebo	REMICADE	Placebo	REMICADE
Rheumatoid arthritis[a]	24%	34%	3%	4%	<1%	<1%
Crohn's disease[b]	34%	39%	4%	5%	0%	2%
Ulcerative colitis[c]	12%	17%	1%	2%	<1%	<1%
Ankylosing spondylitis[d]	15%	51%	0%	10%	0%	4%
Psoriatic arthritis[e]	16%	50%	0%	7%	0%	2%
Plaque psoriasis[f]	24%	49%	<1%	8%	0%	3%

[a] Placebo patients received methotrexate while REMICADE patients received both REMICADE and methotrexate. Median follow-up was 58 weeks. [b] Placebo patients in the 2 Phase 3 trials in Crohn's disease received an initial dose of 5 mg/kg REMICADE at study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo maintenance group and then later crossed over to REMICADE are included in the REMICADE group in ALT analysis. Median follow-up was 54 weeks. [c] Median follow-up was 30 weeks. Specifically, the median duration of follow-up was 30 weeks for placebo and 31 weeks for REMICADE. [d] Median follow-up was 24 weeks for the placebo group and 102 weeks for the REMICADE group. [e] Median follow-up was 39 weeks for the REMICADE group and 18 weeks for the placebo group. [f] ALT values are obtained in 2 Phase 3 psoriasis studies with median follow-up of 50 weeks for REMICADE and 16 weeks for placebo.

Adverse Reactions in Psoriasis Studies: During the placebo-controlled portion across the 3 clinical trials up to week 16, the proportion of patients who experienced at least 1 serious adverse reaction (SAE; defined as resulting in

death, life threatening, requires hospitalization, or persistent or significant disability/incapacity) was 0.5% in the 3 mg/kg REMICADE group, 1.9% in the placebo group, and 1.6% in the 5 mg/kg REMICADE group. Among patients in the 2 Phase 3 studies, 12.4% of patients receiving REMICADE 5 mg/kg every 8 weeks through 1 year of maintenance treatment experienced at least 1 SAE in Study I. In Study II, 4.1% and 4.7% of patients receiving REMICADE 3 mg/kg and 5 mg/kg every 8 weeks, respectively, through 1 year of maintenance treatment experienced at least 1 SAE. One death due to bacterial sepsis occurred 25 days after the second infusion of 5 mg/kg REMICADE. Serious infections included sepsis, and abscesses. In Study I, 2.7% of patients receiving REMICADE 5 mg/kg every 8 weeks through 1 year of maintenance treatment experienced at least 1 serious infection. In Study II, 1.0% and 1.3% of patients receiving REMICADE 3 mg/kg and 5 mg/kg, respectively, through 1 year of treatment experienced at least 1 serious infection. The most common serious infection (requiring hospitalization) was abscess (skin, throat, and peri-rectal) reported by 5 (0.7%) patients in the 5 mg/kg REMICADE group. Two active cases of tuberculosis were reported: 6 weeks and 34 weeks after starting REMICADE. In the placebo-controlled portion of the psoriasis studies, 7 of 1123 patients who received REMICADE at any dose were diagnosed with at least one NMSC compared to 0 of 334 patients who received placebo. In the psoriasis studies, 1% (15/1373) of patients experienced serum sickness or a combination of arthralgia and/or myalgia with fever, and/or rash, usually early in the treatment course. Of these patients, 6 required hospitalization due to fever, severe myalgia, arthralgia, swollen joints, and immobility. ***Other Adverse Reactions:*** Safety data are available from 4779 REMICADE-treated adult patients, including 1304 with rheumatoid arthritis, 1106 with Crohn's disease, 484 with ulcerative colitis, 202 with ankylosing spondylitis, 293 with psoriatic arthritis, 1373 with plaque psoriasis and 17 with other conditions. *[For information on other adverse reactions in pediatric patients, see Adverse Reactions]*. Adverse reactions reported in ≥5% of all patients with rheumatoid arthritis receiving 4 or more infusions are in Table 2. The types and frequencies of adverse reactions observed were similar in REMICADE-treated rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis and Crohn's disease patients except for abdominal pain, which occurred in 26% of REMICADE-treated patients with Crohn's disease. In the Crohn's disease studies, there were insufficient numbers and duration of follow-up for patients who never received REMICADE to provide meaningful comparisons.

Table 2 Adverse reactions occurring in 5% or more of patients receiving 4 or more infusions for rheumatoid arthritis

	Placebo	REMICADE
	(n=350)	(n=1129)
Average weeks of follow-up	59	66
Gastrointestinal		
Nausea	20%	21%
Abdominal pain	8%	12%
Diarrhea	12%	12%
Dyspepsia	7%	10%
Respiratory		
Upper respiratory tract infection	25%	32%
Sinusitis	8%	14%
Pharyngitis	8%	12%
Coughing	8%	12%
Bronchitis	9%	10%
Skin and appendages disorders		
Rash	5%	10%
Pruritus	2%	7%
Body as a whole-general disorders		
Fatigue	7%	9%
Pain	7%	8%
Resistance mechanism disorders		
Fever	4%	7%
Moniliasis	3%	5%
Central and peripheral nervous system disorders		
Headache	14%	18%
Musculoskeletal system disorders		
Arthralgia	7%	8%
Urinary system disorders		
Urinary tract infection	6%	8%
Cardiovascular disorders, general		
Hypertension	5%	7%

The most common serious adverse reactions observed in clinical trials were infections *[see Adverse Reactions]*. Other serious, medically relevant adverse reactions ≥0.2% or clinically significant adverse reactions by body system were as follows: *Body as a whole:* allergic reaction, edema; *Blood:* pancytopenia; *Cardiovascular:* hypotension; *Gastrointestinal:* constipation, intestinal obstruction; *Central and Peripheral Nervous:* dizziness; *Heart Rate and Rhythm:* bradycardia; *Liver and Biliary:* hepatitis; *Metabolic and Nutritional:* dehydration; *Platelet, Bleeding and Clotting:* thrombocytopenia; *Neoplasms:* lymphoma; *Red Blood Cell:* anemia, hemolytic anemia; *Resistance Mechanism:* cellulitis, sepsis, serum sickness, sarcoidosis; *Respiratory:* lower respiratory tract infection (including pneumonia), pleurisy, pulmonary edema; *Skin and Appendages:* increased sweating; *Vascular (Extracardiac):* thrombophlebitis; *White Cell and Reticuloendothelial:* leukopenia, lymphadenopathy. **Adverse Reactions in Pediatric Patients:** ***Pediatric Crohn's Disease:*** There were some differences in the adverse reactions observed in the pediatric patients receiving REMICADE compared to those observed in adults with Crohn's disease. These differences are discussed in the following paragraphs. The following adverse reactions were reported more commonly in 103 randomized pediatric Crohn's disease patients administered 5 mg/kg REMICADE through 54 weeks than in 385 adult Crohn's disease patients receiving a similar treatment regimen: anemia (11%), leukopenia (9%), flushing (9%), viral infection (8%), neutropenia (7%), bone fracture (7%), bacterial infection (6%), and respiratory tract allergic reaction (6%). Infections were reported in 56% of randomized pediatric patients in Study Peds Crohn's and in 50% of adult patients in Study Crohn's I. In Study Peds Crohn's, infections were reported more frequently for patients who received every 8-week as opposed to every 12-week infusions (74% and 38%, respectively), while serious infections were reported for 3 patients in the every 8-week and 4 patients in the every 12-week maintenance treatment group. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was abscess. Pneumonia was reported for 3 patients, (2 in the every 8-week and 1 in the every 12-week maintenance treatment groups). Herpes zoster was reported for 2 patients in the every 8-week maintenance treatment group. In Study Peds Crohn's, 18% of randomized patients experienced 1 or more infusion reactions, with no notable difference between treatment groups. Of the 112 patients in Study Peds Crohn's, there were no serious infusion reactions, and 2 patients had non-serious anaphylactoid reactions. In Study Peds Crohn's, in which all patients received stable doses of 6-MP, AZA, or MTX, excluding inconclusive samples, 3 of 24 patients had antibodies to infliximab. Although 105 patients were tested for antibodies to infliximab, 81 patients were classified as inconclusive because they could not be ruled as negative due to assay interference by the presence of infliximab in the sample. Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 18% of pediatric patients in Crohn's disease clinical trials; 4% had ALT elevations ≥3 x ULN, and 1% had elevations ≥5 x ULN. (Median follow-up was 53 weeks.) ***Pediatric Ulcerative Colitis:*** Overall, the adverse reactions reported in the pediatric ulcerative colitis trial and adult ulcerative colitis (Study UC I and Study UC II) studies were generally consistent. In a pediatric UC trial, the most common adverse reactions were upper respiratory tract infection, pharyngitis, abdominal pain, fever, and headache. Infections were reported in 31 (52%) of 60 treated patients in the pediatric UC trial and 22 (37%) required oral or parenteral antimicrobial treatment. The proportion of patients with infections in the pediatric UC trial was similar to that in the pediatric Crohn's disease study (Study Peds Crohn's) but higher than the proportion in the adults' ulcerative colitis studies (Study UC I and Study UC II). The overall incidence of infections in the pediatric UC trial was 13/22 (59%) in the every 8 week maintenance treatment group. Upper respiratory tract infection (7/60 [12%]) and pharyngitis (5/60 [8%]) were the most frequently reported respiratory system infections. Serious infections were reported in 12% (7/60) of all treated patients. In the pediatric UC trial, excluding inconclusive samples, 4 of 19 patients had antibodies to infliximab. Although 52 patients were tested, 33 patients were classified as inconclusive because they could not be ruled as negative due to assay interference by the presence of infliximab in the sample. Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 17% (10/60) of pediatric patients in the pediatric UC trial; 7% (4/60) had ALT elevations ≥3 x ULN, and 2% (1/60) had elevations ≥5 x ULN (median follow-up was 49 weeks). Overall, 8 of 60 (13%) treated patients experienced one or more infusion reactions, including 4 of 22 (18%) patients in the every 8-week treatment maintenance group. No serious infusion reactions were reported. In the pediatric UC trial, 45 patients were in the 12 to 17 year age group and 15 in the 6 to 11 year age group. The numbers of patients in each subgroup are too small to make any definitive conclusions about the effect of age on safety events. There were higher proportions of patients with serious adverse events (40% vs. 18%) and discontinuation due to adverse events (40% vs. 16%) in the younger age group than in the older age group. While the proportion of patients with infections was also higher in the younger age group (60% vs. 49%), for serious infections, the proportions were similar in the two age groups (13% in the 6 to 11 year age group vs. 11% in the 12 to 17 year age group). Overall proportions of adverse reactions, including infusion reactions, were similar between the 6 to 11 and 12 to 17 year age groups (13%). **Post-marketing Experience:** Adverse reactions have been reported during post approval use of REMICADE in adult and pediatric patients. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to REMICADE exposure. The following adverse reactions, some with fatal outcome, have been reported during post-approval use of REMICADE: neutropenia *[see Warnings and Precautions]*, interstitial lung disease (including pulmonary fibrosis/interstitial pneumonitis and very rare rapidly progressive disease), idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, systemic and cutaneous vasculitis, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy), new onset and worsening psoriasis (all subtypes including pustular, primarily palmoplantar), transverse myelitis, and neuropathies (additional neurologic reactions have also been observed) *[see Warnings and Precautions]*, acute liver failure, jaundice, hepatitis, and cholestasis *[see Warnings and Precautions]*, serious infections *[see Warnings and Precautions]* and malignancies *[see Warnings and Precautions]*. ***Infusion-related Reactions:*** In post-marketing experience, cases of anaphylactic reactions, including laryngeal/pharyngeal edema and severe bronchospasm, and seizure have been associated with REMICADE

REMICADE® (infliximab)

administration. Cases of myocardial ischemia/infarction and transient visual loss have also been rarely reported in association with REMICADE during or within 2 hours of infusion. ***Adverse Reactions in Pediatric Patients:*** The following serious adverse reactions have been reported in the post-marketing experience in children: infections (some fatal) including opportunistic infections and tuberculosis, infusion reactions, and hypersensitivity reactions. Serious adverse reactions in the post-marketing experience with REMICADE in the pediatric population have also included malignancies, including hepatosplenic T-cell lymphomas *[see Boxed WARNINGS and Warnings and Precautions]*, transient hepatic enzyme abnormalities, lupus-like syndromes, and the development of autoantibodies. **DRUG INTERACTIONS: Use with Anakinra or Abatacept:** An increased risk of serious infections was seen in clinical studies of other TNFα-blocking agents used in combination with anakinra or abatacept, with no added clinical benefit. Because of the nature of the adverse reactions seen with these combinations with TNF-blocker therapy, similar toxicities may also result from the combination of anakinra or abatacept with other TNFα-blocking agents. Therefore, the combination of REMICADE and anakinra or abatacept is not recommended *[see Warnings and Precautions]*. **Use with Tocilizumab:** The use of tocilizumab in combination with biological DMARDs such as TNF antagonists, including REMICADE, should be avoided because of the possibility of increased immunosuppression and increased risk of infection. **Methotrexate (MTX) and Other Concomitant Medications:** Specific drug interaction studies, including interactions with MTX, have not been conducted. The majority of patients in rheumatoid arthritis or Crohn's disease clinical studies received one or more concomitant medications. In rheumatoid arthritis, concomitant medications besides MTX were nonsteroidal anti-inflammatory agents (NSAIDs), folic acid, corticosteroids and/or narcotics. Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids, 6-MP/AZA and aminosalicylates. In psoriatic arthritis clinical trials, concomitant medications included MTX in approximately half of the patients as well as NSAIDs, folic acid and corticosteroids. Concomitant MTX use may decrease the incidence of anti-infliximab antibody production and increase infliximab concentrations. **Immunosuppressants:** Patients with Crohn's disease who received immunosuppressants tended to experience fewer infusion reactions compared to patients on no immunosuppressants *[see Adverse Reactions]*. Serum infliximab concentrations appeared to be unaffected by baseline use of medications for the treatment of Crohn's disease including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and aminosalicylates. **Cytochrome P450 Substrates:** The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-1, IL-6, IL-10, IFN) during chronic inflammation. Therefore, it is expected that for a molecule that antagonizes cytokine activity, such as infliximab, the formation of CYP450 enzymes could be normalized. Upon initiation or discontinuation of REMICADE in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed. **USE IN SPECIFIC POPULATIONS: Pregnancy: Pregnancy Category B.:** It is not known whether REMICADE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. REMICADE should be given to a pregnant woman only if clearly needed. Because infliximab does not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with REMICADE. No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα. Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to 40 mg/kg were shown to produce no adverse effects in animal reproduction studies. As with other IgG antibodies, REMICADE crosses the placenta and has been detected up to 6 months in the serum of infants born to female patients treated with REMICADE during pregnancy. Consequently, these infants may be at increased risk of infection, and caution is advised in the administration of live vaccines to these infants *[see Warnings and Precautions]*. **Nursing Mothers:** It is not known whether REMICADE is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from REMICADE, women should not breast-feed their infants while taking REMICADE. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** The safety and effectiveness of REMICADE have been established in pediatric patients 6 to 17 years of age for induction and maintenance treatment of Crohn's disease or ulcerative colitis. However, REMICADE has not been studied in children with Crohn's disease or ulcerative colitis <6 years of age. ***Pediatric Crohn's Disease:*** REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy *[see Boxed Warnings, Warnings and Precautions, Indications and Usage (1.2) in full Prescribing Information, Dosage and Administration (2.2) in full Prescribing Information, Clinical Studies (14.2) in full Prescribing Information, and Adverse Reactions]*. REMICADE has been studied only in combination with conventional immunosuppressive therapy in pediatric Crohn's disease. The longer term (greater than 1 year) safety and effectiveness of REMICADE in pediatric Crohn's disease patients have not been established in clinical trials. ***Pediatric Ulcerative Colitis:*** The safety and effectiveness of REMICADE for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients aged 6 years and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy are supported by evidence from adequate and well-controlled studies of REMICADE in adults. Additional safety and pharmacokinetic data were collected in 60 pediatric patients aged 6 years and older [*see Clinical Pharmacology (12.3) in full Prescribing Information, Dosage and Administration (2.4) in full Prescribing Information, Adverse Reactions, and Clinical Studies, (14.4) in full Prescribing Information*]. The effectiveness of REMICADE in inducing and maintaining mucosal healing could not be established. Although 41 patients had a Mayo endoscopy subscore of 0 or 1 at the Week 8 endoscopy, the induction phase was open-label and lacked a control group. Only 9 patients had an optional endoscopy at Week 54. In the pediatric UC trial, approximately half of the patients were on concomitant immunomodulators (AZA, 6-MP, MTX) at study start. Due to the risk of HSTCL, a careful risk-benefit assessment should be made when REMICADE is used in combination with other immunosuppressants. The longer term (greater than 1 year) safety and effectiveness of REMICADE in pediatric ulcerative colitis patients have not been established in clinical trials. ***Juvenile Rheumatoid Arthritis (JRA):*** The safety and efficacy of REMICADE in patients with juvenile rheumatoid arthritis (JRA) were evaluated in a multicenter, randomized, placebo-controlled, double-blind study for 14 weeks, followed by a double-blind, all-active treatment extension, for a maximum of 44 weeks. Patients with active JRA between the ages of 4 and 17 years who had been treated with MTX for at least 3 months were enrolled. Concurrent use of folic acid, oral corticosteroids (≤0.2 mg/kg/day of prednisone or equivalent), NSAIDs, and/or disease modifying antirheumatic drugs (DMARDs) was permitted. Doses of 3 mg/kg REMICADE or placebo were administered intravenously at Weeks 0, 2 and 6. Patients randomized to placebo crossed-over to receive 6 mg/kg REMICADE at Weeks 14, 16, and 20, and then every 8 weeks through Week 44. Patients who completed the study continued to receive open-label treatment with REMICADE for up to 2 years in a companion extension study. The study failed to establish the efficacy of REMICADE in the treatment of JRA. Key observations in the study included a high placebo response rate and a higher rate of immunogenicity than what has been observed in adults. Additionally, a higher rate of clearance of infliximab was observed than had been observed in adults *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. A total of 60 patients with JRA were treated with doses of 3 mg/kg and 57 patients were treated with doses of 6 mg/kg. The proportion of patients with infusion reactions who received 3 mg/kg REMICADE was 35% (21/60) over 52 weeks compared with 18% (10/57) in patients who received 6 mg/kg over 38 weeks. The most common infusion reactions reported were vomiting, fever, headache, and hypotension. In the 3 mg/kg REMICADE group, 4 patients had a serious infusion reaction and 3 patients reported a possible anaphylactic reaction (2 of which were among the serious infusion reactions). In the 6 mg/kg REMICADE group, 2 patients had a serious infusion reaction, 1 of whom had a possible anaphylactic reaction. Two of the 6 patients who experienced serious infusion reactions received REMICADE by rapid infusion (duration of less than 2 hours). Antibodies to infliximab developed in 38% (20/53) of patients who received 3 mg/kg REMICADE compared with 12% (6/49) of patients who received 6 mg/kg. A total of 68% (41/60) of patients who received 3 mg/kg REMICADE in combination with MTX experienced an infection over 52 weeks compared with 65% (37/57) of patients who received 6 mg/kg REMICADE in combination with MTX over 38 weeks. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was pneumonia. Other notable infections included primary varicella infection in 1 patient and herpes zoster in 1 patient. **Geriatric Use:** In rheumatoid arthritis and plaque psoriasis clinical trials, no overall differences were observed in effectiveness or safety in 181 patients with rheumatoid arthritis and 75 patients with plaque psoriasis, aged 65 or older who received REMICADE, compared to younger patients—although the incidence of serious adverse reactions in patients aged 65 or older was higher in both REMICADE and control groups compared to younger patients. In Crohn's disease, ulcerative colitis, ankylosing spondylitis and psoriatic arthritis studies, there were insufficient numbers of patients aged 65 and over to determine whether they respond differently from patients aged 18 to 65. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly *[see Adverse Reactions]*. **OVERDOSAGE:** Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately. **REFERENCES:** 1. American Thoracic Society, Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2000;161:S221-S247. 2. See latest Centers for Disease Control guidelines and recommendations for tuberculosis testing in immunocompromised patients.

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IMPORTANT SAFETY INFORMATION FOR REMICADE® (cont'd)

The risks and benefits of treatment with REMICADE® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with REMICADE®, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy. Risk of infection may be higher in patients greater than 65 years of age, pediatric patients, patients with co-morbid conditions and/or patients taking concomitant immunosuppressant therapy. In clinical trials, other serious infections observed in patients treated with REMICADE® included pneumonia, cellulitis, abscess, and skin ulceration.

MALIGNANCIES

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including REMICADE®. Approximately half of these cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months after the first dose of therapy. Most of the patients were receiving concomitant immunosuppressants.

Postmarketing cases of hepatosplenic T-cell lymphoma, a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including REMICADE®. These cases have had a very aggressive disease course and have been fatal. All reported REMICADE® cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. All of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with REMICADE® at or prior to diagnosis. Carefully assess the risks and benefits of treatment with REMICADE®, especially in these patient types.

In clinical trials of all TNF inhibitors, more cases of lymphoma were observed compared with controls and the expected rate in the general population. However, patients with Crohn's disease, rheumatoid arthritis, or plaque psoriasis may be at higher risk for developing lymphoma. In clinical trials of some TNF inhibitors, including REMICADE®, more cases of other malignancies were observed compared with controls. The rate of these malignancies among patients treated with REMICADE® was similar to that expected in the general population whereas the rate in control patients was lower than expected. Cases of acute and chronic leukemia have been reported with postmarketing TNF-blocker use. As the potential role of TNF inhibitors in the development of malignancies is not known, caution should be exercised when considering treatment of patients with a current or a past history of malignancy or other risk factors such as chronic obstructive pulmonary disease (COPD).

CONTRAINDICATIONS

REMICADE® is contraindicated in patients with moderate to severe (NYHA Class III/IV) congestive heart failure (CHF) at doses greater than 5 mg/kg. Higher mortality rates at the 10 mg/kg dose and higher rates of cardiovascular events at the 5 mg/kg dose have been observed in these patients. REMICADE® should be used with caution and only after consideration of other treatment options. Patients should be monitored closely. Discontinue REMICADE® if new or worsening CHF symptoms appear. REMICADE® should not be (re)administered to patients who have experienced a severe hypersensitivity reaction or to patients with hypersensitivity to murine proteins or other components of the product.

HEPATITIS B REACTIVATION

TNF inhibitors, including REMICADE®, have been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases were fatal. Patients should be tested for HBV infection before initiating REMICADE®. For patients who test positive, consult a physician with expertise in the treatment of hepatitis B. Exercise caution when prescribing REMICADE® for patients identified as carriers of HBV and monitor closely for active HBV infection during and following termination of therapy with REMICADE®. Discontinue REMICADE® in patients who develop HBV reactivation and initiate antiviral therapy with appropriate supportive treatment. Exercise caution when considering resumption of REMICADE® and monitor patients closely.

HEPATOTOXICITY

Severe hepatic reactions, including acute liver failure, jaundice, hepatitis, and cholestasis have been reported rarely in patients receiving REMICADE® postmarketing. Some cases were fatal or required liver transplant. Aminotransferase elevations were not noted prior to discovery of liver injury in many cases. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (eg, ≥5 times the upper limit of normal) develop, REMICADE® should be discontinued, and a thorough investigation of the abnormality should be undertaken.

HEMATOLOGIC EVENTS

Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia (some fatal) have been reported. The causal relationship to REMICADE® therapy remains unclear. Exercise caution in patients who have ongoing or a history of significant hematologic abnormalities. Advise patients to seek immediate medical attention if they develop signs and symptoms of blood dyscrasias or infection. Consider discontinuation of REMICADE® in patients who develop significant hematologic abnormalities.

HYPERSENSITIVITY

REMICADE® has been associated with hypersensitivity reactions that differ in their time of onset. Acute urticaria, dyspnea, and hypotension have occurred in association with infusions of REMICADE®. Serious infusion reactions including anaphylaxis were infrequent. Medications for the treatment of hypersensitivity reactions should be available.

NEUROLOGIC EVENTS

TNF inhibitors, including REMICADE®, have been associated in rare cases with CNS manifestation of systemic vasculitis, seizure, and new onset or exacerbation of CNS demyelinating disorders, including multiple sclerosis and optic neuritis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. Exercise caution when considering REMICADE® in patients with these disorders and consider discontinuation if these disorders develop.

AUTOIMMUNITY

Treatment with REMICADE® may result in the formation of autoantibodies and, rarely, in development of a lupus-like syndrome. Discontinue treatment if symptoms of a lupus-like syndrome develop.

ADVERSE REACTIONS

In clinical trials, the most common REMICADE® adverse reactions occurring in >10% of patients included infections (eg, upper respiratory, sinusitis, and pharyngitis), infusion-related reactions, headache, and abdominal pain.

USE WITH OTHER DRUGS

The use of REMICADE® in combination with anakinra, abatacept or tocilizumab is not recommended. Care should be taken when switching from one biologic to another, since overlapping biological activity may further increase the risk of infection.

VACCINATIONS

Live vaccines should not be given with REMICADE®. Bring pediatric patients up to date with all vaccinations prior to initiating REMICADE®. Exercise caution in the administration of live vaccines to infants born to female patients treated with REMICADE® during pregnancy.

Please see Brief Summary of full Prescribing Information accompanying this advertisement.

References: 1. REMICADE® Prescribing Information. Janssen Biotech, Inc. **2.** Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2005;353:2462-2476. **3.** American Thoracic Society, Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med*. 2000;161:S221-S247. **4.** See latest Centers for Disease Control guidelines and recommendations for tuberculosis testing in immunocompromised patients.

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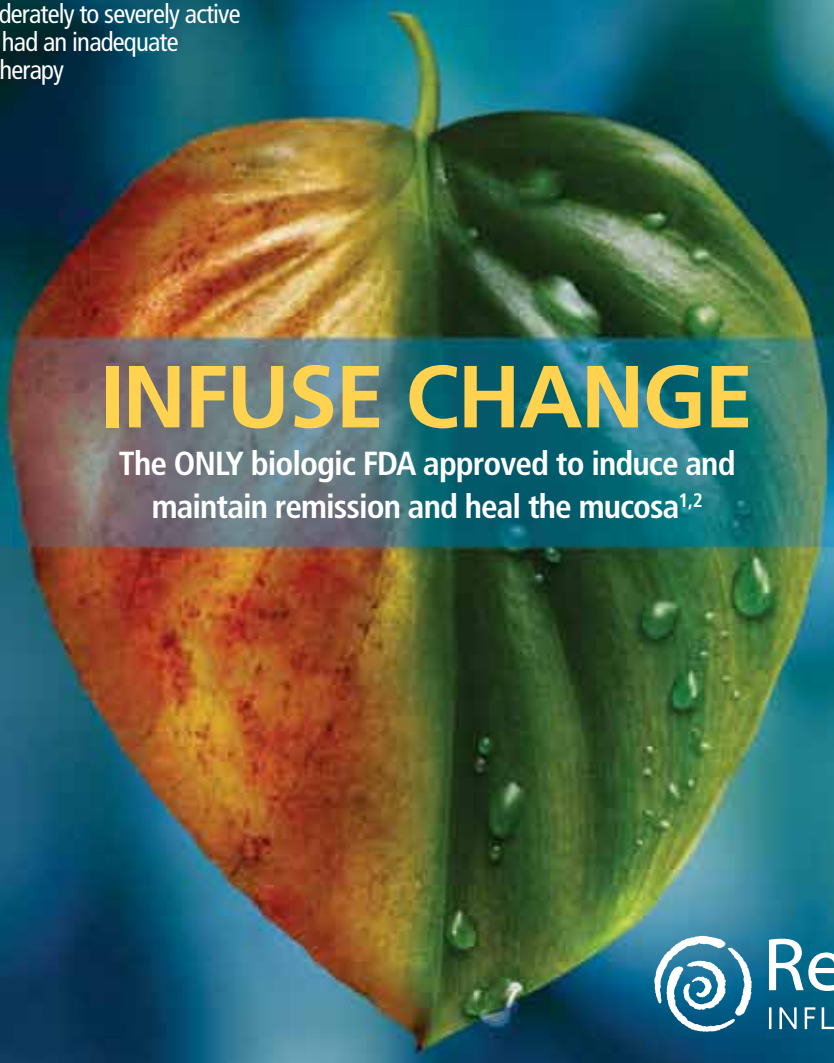
Remicade® INFLIXIMAB

For adult patients with moderately to severely active ulcerative colitis (UC) who had an inadequate response to conventional therapy



INFUSE CHANGE

The ONLY biologic FDA approved to induce and maintain remission and heal the mucosa[1,2]

Remicade®
INFLIXIMAB

REMICADE® is indicated for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

IMPORTANT SAFETY INFORMATION FOR REMICADE® (infliximab)
SERIOUS INFECTIONS

Patients treated with REMICADE® (infliximab) are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Discontinue REMICADE® if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent TB before and during treatment with REMICADE®.[3,4] Treatment for latent infection should be initiated prior to treatment with REMICADE®.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis and pneumocystosis. Patients may present with disseminated, rather than localized, disease. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.**

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