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Progress in the Diagnosis and Treatment of Inflammatory Bowel Disease

A Review of Selected Presentations from Recent Meetings:

- 75th American College of Gastroenterology
  Annual Scientific Meeting and Postgraduate Course
  October 15–20, 2010
  San Antonio, Texas

- 2010 Advances in Inflammatory Bowel Diseases
  Crohn's & Colitis Foundation's
  Clinical and Research Conference
  December 9–12, 2010
  Hollywood, Florida

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Target Audience: This activity has been designed to meet the educational needs of practicing gastroenterologists who wish to review and update their knowledge of recent data presented regarding the treatment of Crohn's disease (CD) and ulcerative colitis (UC).

Statement of Need/Program Overview: A solid interpretation and understanding of new data plays a major role in giving patients the best treatment possible. Due to the ever increasing abundance of new data in this particular therapeutic area in CD and UC, the data and their impact on community practice is relatively misunderstood by physicians and should be clarified and reviewed.

Educational Objectives: After completing this activity, the participant should be better able to:

1. Summarize the current role of biologic and newer therapies in the treatment of moderate-to-severe CD and UC.
2. Discuss emerging data on the use of biologics and newer therapies as they relate to use in clinical practice.
3. Describe new strategies to maximize efficacy and durability of response that improve quality of life in patients with moderate-to-severe CD and UC.

Faculty: Edward V. Loftus, Jr., MD, is Professor of Medicine in the Division of Gastroenterology and Hepatology at Mayo Clinic in Rochester, Minnesota.

Accreditation Statement: This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Postgraduate Institute for Medicine (PIM) and *Gastroenterology & Hepatology*. PIM is accredited by the ACCME to provide continuing medical education for physicians.

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Introduction

Crohn's disease (CD) and ulcerative colitis (UC), the 2 main types of inflammatory bowel disease (IBD), are chronic conditions characterized by active symptom flares alternating with symptom-free periods. Triggered by an underlying idiopathic inflammatory response, the symptoms of CD and UC can include diarrhea, abdominal pain, rectal bleeding, and malnutrition.

Between 1 and 2 million Americans are estimated to have CD or UC. In a population-based study from Olmsted County, Minnesota, the incidence and prevalence of UC were 8.8 cases per 100,000 people per year (95% confidence interval [CI]: 7.2–10.5) and 214 cases per 100,000 people (95% CI: 188–240), respectively. The incidence and prevalence of CD were 7.9 cases per 100,000 people per year (95% CI: 6.3–9.5) and 174 cases per 100,000 people (95% CI: 151–197), respectively.[1] Both UC and CD are diagnosed more frequently in individuals between the ages of 15 and 40 years, with the peak incidence occurring during the third decade of life, but children and elderly individuals are also occasionally diagnosed with IBD.

While the causes of IBD remain unclear, the underlying pathophysiology of the disease can be traced to inflammation of the mucosal lining of the intestinal tract, which leads to ulceration, edema, bleeding, and loss of fluids and electrolytes. Researchers do not yet know exactly what triggers IBD, but many patients may have a genetic component to their disease. *NOD2/CARD15* is an example of 1 genetic linkage that has been associated with a predisposition for CD.[2] IBD is also more common among individuals with a family history of the disease; the age-adjusted risk of IBD is approximately 5% for siblings and 10% for offspring, and children of parents with IBD have a 2- to 30-fold increased risk of developing IBD themselves.[3,4] There is also a much higher concordance of IBD among identical versus fraternal twins.[3]

Among patients with UC, the most common presenting symptom is diarrhea with occult or frank blood loss; UC patients generally do not experience abdominal pain. CD patients also typically present with diarrhea, but often without bleeding, and CD patients more frequently experience abdominal pain, especially if they have an intestinal obstruction. Classically, this pain is localized to the lower abdomen or lower right quadrant, although it may present anywhere. Painful intestinal strictures and obstructions are inflamed and generally require endoscopic or surgical intervention. While strictures are relatively common in CD, colonic strictures are of significant concern in UC because of their malignant potential. While patients with UC generally do not develop fistulae or perianal disease, they may rarely experience perianal abscesses.

In UC, intestinal inflammation is typically restricted to the colon, but CD can affect any portion of the gastrointestinal tract, although the ileum and the colon are the most commonly affected sites. Identifying the area of disease involvement is important, as it largely dictates the types of manifestations that IBD patients experience. In addition to slightly different presentations, CD can often be distinguished from UC on endoscopy, as the 2 conditions show differences in pathology. While the inflammation associated with UC is typically continuous and superficial, affecting only the intestinal mucosa and submucosa, the inflammation associated with CD often exhibits a discontinuous pattern that is transmural.

Conventional Therapy for IBD

Management of both UC and CD relies on a range of medical and surgical interventions, and the chronic nature of IBD means that these conditions generally require long-term treatment. Because CD can manifest in any part of the gastrointestinal tract and because it can recur postoperatively, surgery is not curative for this condition; surgery to remove the colon is considered curative for UC, but it is not a treatment of choice for most patients. Nonetheless, 60–80% of CD patients and up to 30% of UC patients eventually require surgical resection to remove some or all of the diseased intestinal tissue.[5] Whenever possible, however, the majority of IBD patients turn to pharmacologic agents to manage their disease. The main goals of medical treatment for IBD include induction and maintenance of remission, as well as improvement in patients' quality of life (QOL).

Aminosalicylates are often a first step in the medical management of IBD, and they are the mainstay of therapy for UC. Unfortunately, these agents frequently have limited efficacy, especially in CD; either they are not strong enough to induce remission in moderately to severely active disease, or they are initially effective but patients subsequently lose response.

Corticosteroids are also used as an initial therapy for the management of moderate-to-severe IBD. These agents offer rapid relief of symptoms and a significant decrease

in inflammation, but they are associated with significant adverse effects, including bone damage and risk of infection. In a population-based study, corticosteroid therapy was shown to rapidly alter the natural history of the disease, with over half (58%) of patients achieving remission immediately.[6] However, only 32% of CD patients were able to maintain disease-free remission at 1 year after the first course of corticosteroids, and 28% of patients developed corticosteroid-dependence over the course of the year.

For this reason, immunomodulators are often used for maintenance of remission following induction therapy with corticosteroids. In North America, the immunomodulators most widely used for IBD are 6-mercaptopurine (6-MP); its prodrug, azathioprine; and methotrexate. While effective, these agents have a slow onset of action and a narrow therapeutic window.

Biologics for Treatment of IBD

The poor safety profiles associated with corticosteroids and immunomodulatory agents plus the frequent development of resistance to both types of drugs has created a need for the development of alternative agents that can be used to treat patients with moderate-to-severe IBD. Biologic agents for the treatment of IBD consist of therapies directed against the tumor necrosis factor (TNF)-α cytokine, an important component in the pathogenesis of IBD.[7] Several of these biologic agents are now approved by the US Food and Drug Administration (FDA) for varying indications. Infliximab was the first anti-TNF agent to gain approval for use in IBD; it is approved for treatment of moderate-to-severe CD in patients who have not responded well to other therapies, for reducing the number of draining enterocutaneous and rectovaginal fistulas, and for maintaining fistula closure in adults with CD. Infliximab is also approved for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to severely active UC who had an inadequate response to conventional therapy.

Since the approval of infliximab, several other anti-TNF-α agents have been developed for use in IBD, including adalimumab, a fully human monoclonal antibody to TNF-α, and certolizumab pegol, a pegylated, humanized Fab' fragment of an anti-TNF antibody. Currently, adalimumab and certolizumab pegol are only approved for the treatment of CD patients; adalimumab is also indicated for adults who are unable to tolerate or have lost response to infliximab.

Finally, TNF-α is not the only molecule under investigation as a target for IBD treatments. For example, the monoclonal antibody natalizumab is directed against the cellular adhesion molecule α4-integrin, an important mediator of leukocyte migration and infiltration into the intestinal lining.[8] Hopefully, more treatment options will become available as ongoing research provides additional targets for IBD therapy.

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Highlights from the 2010 ACG and Advances in IBD Meetings

Adalimumab Studies

Effect of Disease Duration on "Deep Remission": Results from the EXTEND Trial[1]

J-F Colombel, S Schreiber, P Rutgeerts, WJ Sandborn, M Yang, KG Lomax, PF Pollack, RB Thakkar, A Camez, B Huang, Q Zhou, PM Mulani, J Chao

Studies have shown that adalimumab is effective for the induction and maintenance of remission in CD patients with moderately to severely active disease who had an inadequate response to conventional therapy or who lost response or became intolerant to infliximab.[2-4] However, the CHARM trial showed that adalimumab yielded higher rates of clinical remission among patients with a shorter duration of CD.[5] Therefore, the current study evaluated patients from the EXTEND study to determine the relationship between CD duration and rate of "deep remission" (defined as achieving mucosal healing and a Crohn's Disease Activity Index [CDAI] score <150 points).

In the EXTEND trial, 135 patients received open-label adalimumab at Week 0 (160 mg) and Week 2 (80 mg). At Week 4, patients were randomized to receive either adalimumab (40 mg every other week) or placebo, and this treatment was continued until Week 52. After Week 8, patients who experienced a flare or nonresponse were eligible to receive open-label adalimumab (40 mg every other week); those with continued flares or nonresponse could receive a higher dose of adalimumab (40 mg weekly). All patients had been diagnosed with CD at least 4 months previously; disease durations were 2 years or less (14%), more than 2 years to 5 years (20%), and more than 5 years (66%).

More patients in the adalimumab group compared to the placebo group achieved deep remission at Week 52, after stratifying by CD duration: 25% versus 0% in patients with a disease duration of 5 years or less and 16% versus 0% in patients with a disease duration greater than 5 years (P=.009 and P=.008, respectively; Table 1). At Week 12, there was a trend toward improved rates of deep remission with adalimumab among patients with a shorter duration of CD, but this difference was not statistically significant compared to placebo (P<.191).

Table 1. Rate of "Deep Remission"‡ at Week 52

CD duration (years)	Placebo n/N (%)	Adalimumab n/N (%)	*P*-value†
≤2	0/9 (0.0)	3/9 (33.3)	<.001*
>2–≤5	0/15 (0.0)	2/11 (18.2)	
>5	0/41 (0.0)	7/44 (15.9)	

‡Complete mucosal healing (judged by the endoscopist) and clinical remission (CDAI <150).

†Vs placebo, adjusted for baseline disease duration (Cochran-Mantel-Haenszel test).

*Statistically significant.

CD=Crohn's disease; CDAI=Crohn's Disease Activity Index.

The study authors concluded that maintenance therapy with adalimumab resulted in higher rates of deep remission at Week 52 compared to placebo, and this effect occurred regardless of disease duration.

Effect of Adalimumab Induction Therapy on Clinical Laboratory Parameters Suggesting Improved Nutrition and Inflammation Status in Patients with Moderately to Severely Active Ulcerative Colitis[6]

W Reinisch, WJ Sandborn, D Hommes, RB Thakkar, PF Pollack, A Kumar, W Kampman, A Lazar

Anemia and malnutrition are common systemic complications of acute IBD. The prevalence of anemia in IBD patients has been reported to be as high as 74%, and nutritional deficiencies occur in 20–85% of IBD patients, depending on extent, duration, and inflammatory activity.[7-9] Both anemia and malnutrition can negatively affect clinical status and QOL in IBD patients. Because disease severity and activity impact the development of anemia and malnutrition, treatment of the underlying disease may help to improve these complications. In this study, Reinisch and colleagues investigated whether adalimumab could improve anemia and malnutrition in patients with UC.

This randomized, placebo-controlled study of adalimumab for induction of remission enrolled UC patients who had active disease (Mayo score of 6–12 and endoscopy subscore of 2–3) despite concurrent treatment with oral corticosteroids and/or immunosuppressants. Concurrent therapy was not required if patients had received corticosteroids and/or immunosuppressants within the past 5 years and had failed or were intolerant to these therapies. Patients with prior anti-TNF exposure were ineligible for this study.

Following an initial screening period, patients were randomized to receive either 160/80 mg adalimumab (160 mg at Week 0; 80 mg at Week 2; 40 mg at Weeks 4 and 6) or placebo. After initiation of the study, the protocol was modified to include a third treatment arm: 80/40 mg adalimumab (80 mg at Week 0; 40 mg at Weeks 2, 4, and 6). Blood was collected at baseline and Weeks 4 and 8; Mayo scores were assessed at baseline and Week 8.

At Week 8, a significantly higher proportion of patients in the 160/80 mg adalimumab arm achieved clinical remission compared to placebo (15.7% vs 7.2%; *P*=.005). Patients in the 160/80 mg adalimumab arm also achieved a significant improvement in C-reactive protein (CRP) levels compared to placebo (median change from baseline: –0.87 mg/L vs –0.10 mg/L; *P*<.001). Patients in the 80/40 mg adalimumab arm exhibited nonsignificant improvements in clinical remission and CRP levels.

Patients in both the 160/80 mg and 80/40 mg adalimumab arms achieved significant improvements in hemoglobin levels at Week 8 compared to placebo (Table 2). Similarly, both the 160/80 mg and 80/40 mg adalimumab arms showed significant improvements in mean change in hematocrit fraction and mean change in red blood cell count compared to placebo. A comparable proportion of patients in all 3 arms were treated for anemia at least once during the study (15.3%, 19.2%, and 13.0% in the 160/80 mg adalimumab, 80/40 mg adalimumab, and placebo arms, respectively).

Patients in both the 160/80 mg and 80/40 mg adalimumab arms also achieved greater changes in serum total protein and serum albumin levels compared to placebo. The mean changes from baseline in serum total protein were 1.7 g/L, 1.5 g/L, and 0.4 g/L in the 160/80 mg adalimumab, 80/40 mg adalimumab, and placebo arms, respectively (*P*<.01 for 160/80 mg adalimumab vs placebo; *P*<.05 for 80/40 mg adalimumab vs placebo). Mean changes from baseline in serum albumin levels were 1.7 g/L, 1.3 g/L, and 0.7 g/L in the 160/80 mg adalimumab, 80/40 mg adalimumab, and placebo arms, respectively (*P*<.01 for 160/80 mg adalimumab vs placebo). Again, a comparable proportion of patients in all 3 arms received treatment for malnutrition at least once during the study (18.8%, 21.5%, and 18.8% in the 160/80 mg adalimumab, 80/40 mg adalimumab, and placebo arms, respectively). The study authors concluded that induction therapy with adalimumab was associated with significant improvements in both hematologic and nutritional status, as well as improvements in inflammatory indicators and clinical remission.

Table 2. Mean Change in Clinical Laboratory Parameters at Week 8

Change from baseline[a]	Placebo	80/40 mg ADA	160/80 mg ADA
Hemoglobin (g/L)	–0.1	4.4*	4.9*
Hematocrit (fraction)	–0.001	0.014*	0.014*
Red blood cells ($\times 10^{12}$/L)	0.05	0.16†	0.19*
Total protein (g/L)	0.4	1.5‡	1.7†
Albumin (g/L)	0.7	1.3	1.7†
CRP (mg/L)[b]	–0.10	–0.47	–0.87*

[a]Mean changes, except median change for CRP.

[b]Excludes 1 patient without confirmed UC at baseline.

*P<.001

†P<.01

‡P<.05

ADA=adalimumab; CRP=C-reactive protein; UC=ulcerative colitis.

Adalimumab Induction Therapy Improves Health-Related Quality of Life in Patients with Moderately to Severely Active Ulcerative Colitis[10]

WJ Sandborn, W Reinisch, RB Thakkar, A Lazar, B Huang, PM Mulani, J Chao

Health-related QOL is a useful indicator in UC, as QOL worsens during relapse and improves with effective treatment and remission.[11-13] In the current study, Sandborn and colleagues investigated the effect of adalimumab induction therapy on health-related QOL in patients with moderately to severely active UC.

This was a multicenter, double-blind, phase III trial in which 390 patients with moderately to severely active UC were randomized to receive 1 of 3 regimens: 160/80 mg adalimumab (160 mg at Week 0; 80 mg at Week 2; 40 mg at Weeks 4 and 6), 80/40 mg adalimumab (80 mg at Week 0; 40 mg at Weeks 2, 4, and 6), or placebo. Patients were allowed to continue concomitant UC-related medications. All patients were anti-TNF–naïve and had a confirmed UC diagnosis at least 90 days prior to study enrollment. Patients had active disease (Mayo score of 6–12 and endoscopy subscore of 2–3)

despite concurrent therapy with oral corticosteroids and/or immunosuppressants; concurrent therapy was not required if patients had received corticosteroids or immunosuppressants within the past 5 years and had failed to respond or were intolerant to these therapies. Health-related QOL was assessed at baseline and at Weeks 4 and 8 using 2 measurements: the 32-item Inflammatory Bowel Disease Questionnaire (IBDQ; score range 32–224) and the Mental Component Summary and Physical Component Summary (PCS) subscores of the Short Form-36 (SF-36) Health Survey (mean norm-based scores for the general US population are 50±10).[14-16]

Using the last observation carried forward, both assessment tools found significant improvements in health-related QOL at Weeks 4 and 8 for 160/80 mg adalimumab compared to placebo. The 160/80 mg adalimumab arm showed significant improvements compared to placebo in mean IBDQ scores at Week 4 (163 vs 146; $P<.001$) and Week 8 (168 vs 152; $P<.01$) and mean SF-36 PCS scores at Week 4 (47 vs 43; $P<.001$) and Week 8 (49 vs 44; $P<.001$; Table 3). These improvements occurred regardless of baseline CRP concentration (<10 mg/L vs ≥10 mg/L). The significant improvements in mean SF-36 PCS scores at Weeks 4 and 8 also occurred regardless of the patient's weight at baseline; however, the significant mean improvements in mean IBDQ score at Weeks 4 and 8 were apparent only in patients who weighed less than 70 kg at baseline, not in those who weighed 70 kg or more.

Overall, the magnitude of the effect on both mean IBDQ and mean SF-36 PCS scores was numerically larger among patients in the 160/80 mg adalimumab group who had elevated baseline CRP levels (≥10 mg/L) as well as those weighing less than 70 kg. The only evidence of significant improvement in health-related QOL among patients treated with 80/40 mg adalimumab occurred in the SF-36 PCS score at Week 4.

Table 3. Mean Health-related Quality-of-Life Scores (Last Observation Carried Forward)

	Placebo	80/40 mg Adalimumab	160/80 mg Adalimumab
IBDQ			
Baseline	125	126	132
Week 4	146	149	163[a]
Week 8	152	153	168[b]
SF-36 PCS			
Baseline	40	41	42
Week 4	43	45[c]	47[a]
Week 8	44	46	49[a]

[a]$P<.001$ vs placebo.

[b]$P<.01$ vs placebo.

[c]$P<.05$ vs placebo.

IBDQ=Inflammatory Bowel Disease Questionnaire; SF-36 PCS=Short Form-36 Physical Component Summary.

Certolizumab Pegol Studies

Health-Related Quality of Life Improvements in Patients with Active Crohn's Disease Following Treatment with Certolizumab Pegol in the MUSIC Study (NCT00297648)[17]

X Hébuterne, M Lémann, G Coteur, E Ernault, J-F Colombel

Health-related QOL is also an important indicator in CD, as it has been shown to directly correlate with CD activity.[18] In studies evaluating anti-TNF biologic agents, researchers have demonstrated that health-related QOL correlates with clinical improvement, defined as an increase in CDAI.[19-21] In this study, Hébuterne and colleagues assessed health-related QOL among patients in the MUSIC study, a prospective, open-label trial of patients with severely active CD.

All 89 patients in the MUSIC study (mean age 30.2±9.9 years) were treated with open-label 400 mg certolizumab pegol; patients received 3 doses at 2-week intervals and then were dosed every 2–4 weeks for up to 54 weeks. IBDQ scores were used to measure QOL at baseline and at Weeks 10 and 54; missing data were considered to be a nonresponse. Endoscopies were also performed at baseline and at Weeks 10 and 54; endoscopies were scored using the Crohn's Disease Endoscopic Index of Severity (CDEIS).[22] IBDQ response was defined as an increase in IBDQ total score of at least 16 points, and IBDQ remission was defined as a total IBDQ score of 170 points or greater.

At baseline, the mean total IBDQ score was 120.4±28.9 points; mean IBDQ subscores were 38.3±9.4 points for bowel symptoms, 16.1±4.9 points for systemic symptoms, 46.7±12.9 points for emotional function, and 19.2±7.5 points for social function. Mean changes in total IBDQ scores from baseline were 43.8 points and 44.1 points at Weeks 10 and 54, respectively. Improvements occurred in all 4 IBDQ subscores and were similar between Weeks 10 and 54. A high proportion of patients at Weeks 10 and 54 achieved IBDQ response (66.3% and 43.8%, respectively) and IBDQ remission (43.8% and 29.2%, respectively). Importantly, rates of IBDQ remission correlated with rates of CDEIS remission among the intent-to-treat population with available endoscopic

assessments at Weeks 10 and 54; 69.7% of patients in CDEIS remission at Week 10 were also in IBDQ remission, and 60.0% of patients in CDEIS remission at Week 54 were also in IBDQ remission.

The authors concluded that certolizumab pegol induced a substantial improvement in health-related QOL, with improvements that were rapid and sustained over 1 year. Higher IBDQ remission rates among patients who also achieved CDEIS remission demonstrated an association between health-related QOL and clinical improvement.

Long-Term Remission with Certolizumab Pegol in Crohn's Disease: Efficacy Over 4.5 Years in Patients with No Prior TNF Inhibitor Exposure (PRECiSE 3 Study)[23]

GR Lichtenstein, O Thomsen, S Schreiber, IC Lawrance, SB Hanauer, R Bloomfield, WJ Sandborn

The PRECiSE clinical trial program began with 2 phase III studies: PRECiSE 1 demonstrated the efficacy of certolizumab pegol for induction and maintenance of CD in patients with moderately to severely active disease, and PRECiSE 2 showed that certolizumab pegol was effective as maintenance therapy in patients who responded to open-label induction therapy with certolizumab pegol.[24,25] However, up to half of patients who respond to anti-TNF induction therapy develop secondary failure during the subsequent 6–12 months, defined as a loss of response and/or the occurrence of acute or delayed hypersensitivity or injection site reactions.[2,25,26] Thus, the PRECiSE 3 and 4 studies were designed to evaluate the long-term safety and efficacy of certolizumab pegol in CD; these ongoing, open-label trials are continuing to follow patients from PRECiSE 1 and 2. In this abstract, Lichtenstein and colleagues reported interim results from PRECiSE 3.

The PRECiSE 3 study included 141 patients (mean age 37.6±11.9 years) who were randomized to certolizumab pegol and completed an initial 26 weeks of therapy during the PRECiSE 2 study. At the time of enrollment into PRECiSE 2, all patients had moderately to severely active CD (CDAI score of 220–450). During the PRECiSE 3 study, patients continued to receive open-label certolizumab pegol at a dose of 400 mg every 4 weeks. Approximately 80% of patients in the PRECiSE 3 study were infliximab-naïve.

During PRECiSE 3, patients were permitted to withdraw from the study at any time, and they were required to withdraw if they experienced disease exacerbation requiring defined rescue therapy, if their clinical condition warranted discontinuation, or if they failed to comply with the study protocol. In this interim analysis, the data cutoff was at 4.5 years (4 years after completing PRECiSE 2); at this time, only 32% of patients were still on study.

At the beginning of PRECiSE 3, remission was attained in 75% and 78% of total and infliximab-naïve patients, respectively. Clinical remission (defined as Harvey-Bradshaw Index score ≤4) was maintained over the next 4.5 years and was similar between the total and infliximab-naïve patient populations. Remission rates at 1, 2, 3, 4, and 4.5 years were 69%, 69%, 64%, 64%, and 63%, respectively, among the total population and 69%, 68%, 65%, 65%, and 63%, respectively, among the infliximab-naïve population. The majority of adverse events reported during the PRECiSE 3 study were mild or moderate. Of the 50 serious adverse events reported, 13% were serious infections, 2% were tuberculosis, and 2% were malignancies.

The study authors concluded that continuous treatment with certolizumab pegol was effective in patients with moderately to severely active CD, resulting in long-term remission in patients who initially responded to treatment. Further, no new toxicities were observed, leading the authors to suggest that long-term maintenance therapy with certolizumab pegol is also safe.

Induction Therapy with Certolizumab Pegol in Patients with Moderate to Severe Crohn's Disease: A Placebo-Controlled Trial[27]

W Sandborn, S Schreiber, B Feagan, P Rutgeerts, Z Younes, R Bloomfield, J Pablo Guzman, G D'Haens

In 2008, the FDA approved certolizumab pegol for the treatment of patients with moderately to severely active CD who had an inadequate response to conventional therapy. This approval was based largely on positive results from the PRECiSE 1 and 2 studies, which showed that certolizumab pegol could reduce signs and symptoms and maintain response among patients with moderately to severely active CD.[24,25] In the current study, Sandborn and colleagues reported on a phase IIIb, multinational, randomized, double-blind, placebo-controlled clinical trial that further evaluated certolizumab pegol for the induction of clinical remission in this patient population.

A total of 439 patients aged 18–75 years were randomized to receive 400 mg certolizumab pegol or pla-

Table 4. Clinical Remission and Response Rates

Clinical remission (CDAI score ≤150), n (%)			
Week	**Placebo (n=209)**	**400 mg CZP (n=215)**	***P*-value**
2	33 (15.8)	50 (23.3)	.033
4	40 (19.1)	57 (26.5)	.063
6	53 (25.4)	68 (31.6)	.174
Clinical response (decrease in CDAI score ≥100 from Week 0), n (%)			
Week	**Placebo (n=209)**	**400 mg CZP (n=215)**	***P*-value**
2	42 (20.1)	71 (33.0)	.001
4	55 (26.3)	76 (35.3)	.024
6	71 (34.0)	87 (40.5)	.179

CDAI=Crohn's Disease Activity Index; CZP=certolizumab pegol.

cebo, both of which were administered subcutaneously at Weeks 0, 2, and 4. All enrolled patients had moderately to severely active CD (CDAI score of 220–450) and had not received prior anti-TNF therapy. The primary endpoint of the study was the rate of remission (defined as a CDAI score ≤150 points) at Week 6.

Among the intent-to-treat population, there was no significant difference in the rate of clinical remission at Week 6 between certolizumab pegol and placebo (31.6% vs 25.4%; *P*=.174; Table 4). However, remission rates at Week 6 were significantly improved with certolizumab pegol compared to placebo among the subgroup of patients with baseline CRP levels at or above 5 mg/L (33.8% vs 22.5%; *P*<.05). Clinical response (defined as a decrease in CDAI score of ≥100 points from Week 0) was achieved in a significantly higher percentage of patients in the certolizumab pegol group at Week 2 (33.0% vs 20.1%; *P*=.001) and Week 4 (35.3% vs 26.3%; *P*=.024) but not at Week 6 (40.5% vs 34.0%; *P*=.179). No new toxicities were observed with certolizumab pegol.

In this study, certolizumab pegol induction therapy was unable to induce clinical remission at Week 6. However, the authors noted that Week 6 remission was significantly greater among patients with elevated CRP levels, suggesting that inclusion criteria for randomized, controlled clinical trials in IBD need to include an objective assessment of the extent of disease activity.

Infliximab Studies

Single-Center 12-Year Experience with Infliximab[28]

I Shafran, P Burgunder

Infliximab is commonly used to induce and maintain remission in CD, but some patients either fail to respond to infliximab or lose response over time. While multiple previous reports have attempted to define demographic and disease-related factors associated with nonresponse, the results of these studies are conflicting.[29-32] Therefore, this study aimed to identify factors that affect response to infliximab among CD patients in a single-center community practice.

In a retrospective chart review, 125 CD patients who had received at least 1 infliximab infusion between January 1, 1998 and August 12, 2010 were identified at a single IBD treatment center; the standard dosing schedule for infliximab was 5 mg/kg at Weeks 0, 2, and 6. Patients were classified as responders (patients who responded to infliximab after 3 infusions; N=87), primary nonresponders (patients who did not respond after 3 infusions; N=25), or secondary nonresponders (patients who responded to initial therapy but lost response during the maintenance period; N=36).

There were few differences in gender among responders (44% male vs 56% female) and primary nonresponders (56% male vs 44% female); however, secondary nonresponders were mostly female (72% female vs 28% male). Patients in the primary nonresponder group were more likely to have fibrostenotic disease than those in the responder or secondary nonresponder groups (68% vs 38% and 53%, respectively). Similar proportions of patients in the responder and secondary nonresponder groups had penetrating disease (60% and 61%, respectively) and fistulizing disease (54% and 53%, respectively). Smoking was more prevalent among primary and secondary nonresponders compared to responders (36% and 28% vs 23%, respectively), but narcotic use was similar in all 3 groups (12%, 11%, and 12%, respectively). More primary nonresponders had disease restricted to the small bowel compared to responders and secondary nonresponders (40% vs 26% and 25%, respectively), while responders had a higher likelihood of disease restricted to the colon compared to primary and secondary nonresponders (26% vs 12% and 17%, respectively). Disease localization in both the small bowel and colon was prevalent in all 3 groups (46%, 48%, and 56% for responders, primary nonresponders, and secondary nonresponders, respectively). Although this study was limited by a lack of statistical analysis, the investigators concluded that several

characteristics may be predictive of primary nonresponse to infliximab: smoking, fibrostenotic disease, and localization of disease to the small bowel only.

Predictors of Early and Sustained Response to Infliximab in Patients with Ulcerative Colitis[33]

E Rostholder, A Ahmed, A Moss

In another study designed to evaluate predictors associated with response to infliximab, Rostholder and colleagues conducted a retrospective study of UC patients in which demographic, clinical, and biochemical variables were examined. Of 62 patients with complete data, 77% had a primary response to infliximab, 40% were in remission at 12 months, and 35% required colectomy within the 12-month study period. Factors associated with primary response to infliximab in a univariate analysis included age, disease duration, and prior use of azathioprine or 6-MP. Concomitant treatment with azathioprine or 6-MP was not associated with the likelihood of attaining remission or steroid-free remission at 12 months.

Disease duration was significantly associated with risk of progression to colectomy. Compared with patients diagnosed with UC within the past 2 years, those diagnosed at least 2 years previously were 80% less likely to progress to colectomy (95% CI, 0.1–0.6).

Half of the patients in the study (31 of 62) had steroid-refractory disease; among these cases, 65% of patients treated with infliximab had a primary response, 32% were in remission at 12 months, and 42% required colectomy. There was no association between concurrent azathioprine or 6-MP use and primary response to infliximab in these patients. However, age and disease duration remained significant factors.

Clinical Utility of Infliximab in Treating Acute Exacerbation of Crohn's Disease in Treatment Naïve Patients[34]

S Tyagi, M Cannon

The use of infliximab among patients who have been hospitalized for acute exacerbations of CD or UC has not been well studied. To characterize the use of infliximab in an inpatient setting, Tyagi and Cannon conducted a retrospective review of electronic medical records for all patients admitted to the William Beaumont Hospital in Royal Oak, Michigan with an acute flare of CD or UC who subsequently received infliximab on an inpatient basis between January 2007 and September 2009. These patients had not previously received anti-TNF therapy. Of the 2,000 patient records reviewed, 47 eligible patients were evaluated.

Among the 24 patients with CD, 22 (92%) showed a response to infliximab, defined as relief from or resolution of symptoms resulting in early discharge and outpatient follow-up 6–8 weeks later for the next treatment dose. The remaining 8% of patients were nonresponders, defined as patients who required a prolonged hospital stay or surgery. Of the responding patients with CD, fistulizing disease was present in 32%, ileal involvement was present in 44%, and segmental disease was present in 24%.

Among the 23 patients with UC, 17 (74%) responded to infliximab. Factors associated with lack of response in these patients included smoking (odds ratio [OR], 7.14) and prior use of immunosuppressants (OR, 3.25).

Other Noteworthy Studies

Differentiating Crohn's Disease from Ulcerative Colitis: Novel Multi-Genic Disease Markers Validated and Mapped onto Functional Pathways[35]

C Harris, A Treloar, J Alsobrook, L Davis

The differential diagnosis of CD and UC can be difficult given the overlapping clinical signs and symptoms of these 2 conditions and the need for endoscopy with biopsy to make a conclusive determination between them. However, correctly discriminating between CD and UC is necessary to ensure patients receive optimal therapy. Therefore, efforts are underway to determine a molecular signature for each disease. In this study, Harris and colleagues reported results from a study that supports the identification of a gene expression biomarker set that can accurately differentiate between CD and UC.

Using proprietary data mining software that makes no a priori assumptions about biological relationships, researchers analyzed the peripheral blood expression microarray datasets of 59 CD patients and 26 UC patients, each of whom had been diagnosed using endoscopy with biopsy. These datasets were initially divided into a training set (consisting of 28 CD patients and 15 UC patients) and a test set (consisting of 31 CD patients and 11 UC patients). Expression levels of 4,723 gene combinations, consisting of 878 unique genes, were identified as being significantly different between CD and UC. This gene set was then refined to enrich for genes associated with positive regulation of apoptosis (P=.007), general regulation of apoptosis (P=.012), and prostanoid or prostaglandin receptors (P=.05). The gene combinations with the top

scores (accuracy >99% and >90% for training and test sets, respectively) were used to define a list of 10 genes; these genes were then used in a prospective clinical study.

In this clinical study, peripheral blood specimens were collected from 97 CD patients and 95 UC patients whose diagnosis was confirmed by radiology, endoscopy, and biopsy. Blood samples were processed via polymerase chain reaction. Using samples from the clinical study, the researchers defined an optimal classifier set of 3 genes: *MMD*, *DNAJA1*, and *CD4*. This 3-gene set was demonstrated to have sensitivities for CD and UC of 92% and 87%, respectively, and specificities of 87% and 92%, respectively. The positive predictive value and negative predictive value of the 3-gene set for CD were 88% and 91%, respectively; for UC, they were 91% and 88%, respectively.

Each of these 3 genes has previously been found to have a biological role in the differential pathophysiology of CD and UC. For example, the *MMD* (monocyte-to-macrophage differentiation-associated) gene, which is expressed in macrophages but not in undifferentiated monocytes, has a role consistent with the development of CD, in which a macrophage defect results in the production of cytokines but an inability to release them, leading to an impaired acute inflammatory response, delayed bacterial clearance, and granuloma formation.[36,37] The *DNAJA1* gene, like other heat-shock proteins, may be more highly expressed in UC than CD in areas of inflamed mucosa and colonic tissue.[38] Finally, the *CD4* gene has been reported to play a role in T-cell differentiation and activation, and it may be involved in the differential pathophysiology observed between CD and UC.[39] Based on these results, the study authors concluded that this 3-gene expression set (comprised of *MMD*, *DNAJA1*, and *CD4*) could accurately differentiate between CD and UC in a prospective clinical trial.

Update: Meta-Analysis of Overall Risk for Lymphoma with Immunomodulators for Inflammatory Bowel Disease[40]

D Kotlyar, C Brensinger, J Lewis, W Blonski, M Van Domselaar, D Porter, S Sandilya, G Lichtenstein

Development of lymphoma is a rare but serious adverse event that has been associated with immunomodulator treatment for IBD. In a previous meta-analysis, use of azathioprine and 6-MP for treatment of IBD was associated with a 4.18-fold increased risk of lymphoma.[41] However, the utility of this finding was limited since referral data were combined with 1 population-based study, and the incidence of lymphoma in referral centers may be artificially high due to the presence of sicker patients with more comorbidities.[42] Thus, Kotlyar and colleagues revised a previously reported meta-analysis using updated data from an examination of the UK General Practice Research Database.[43,44] Here, the authors directly compared referral center and population-based data.

A total of 6 studies involving referral centers and 2 studies involving population-based data were included

Table 5. Meta-Analysis of Standardized Incidence Ratios (SIR)

Referral center study	Observed	Expected	SIR	95% CI	Number of patients
Connell (PMID: 7910274)	0	0.52	0	NA	755
Farrell (PMID: 10986211)	2	0.05	37.5	(3.53–138)	238*
Fraser (PMID:12144571)	3	0.65	4.64	(0.87–13.7)	626
Kinlen (*Am J Med.* 1985;78:44-49)	2	0.16	12.5	(1.18–46.0)	321
Korelitz (PMID: 10566724)	3	0.61	4.91	(0.93–14.5)	486
Van Domselaar (PMID: 19889478)	5	1.23	4.07	(1.28–9.56)	345
Combined	15	3.22	4.66	(2.60–7.70)	2,771
Population-based study					
Armstrong (PMID: 20104215)	4	1.24	3.23	(0.84–8.34)	1,955
Beaugerie (PMID: 19837455)	17	3.58	4.75	(2.76–7.62)	8,676
Combined	21	4.82	4.36	(2.69–6.67)	10,631
Overall data					
All studies	36	8.04	4.48	(3.13–6.20)	13,402

CI=confidence interval; NA=not applicable; PMID=PubMed identifier.

*As calculated by Kandiel, et al.[41]

in this meta-analysis (Table 5). Among the referral center and population-based studies, pooled standardized incidence ratios were 4.66 (95% CI: 2.60–7.70) and 4.36 (95% CI: 2.69–6.67), respectively; there was no significant difference between the 2 groups (*P*=.84). Significant heterogeneity was observed among the referral center studies (*P*=.047), with standardized incidence ratios ranging from 0 to 37.5 (95% CI: 3.53–138). The overall standardized incidence ratio among both referral center studies and population-based studies was 4.48 (95% CI: 3.13–6.20).

The authors concluded that the overall risk of lymphoma associated with the use of immunomodulators in IBD patients is 4.48-fold higher than that of the general population. Despite prior indications that this rate may be artificially inflated in referral centers, the incidence is similar to that found in population-based studies.

Use of Anti-TNF Therapy is Associated with Decreased Utilization of Diagnostic Imaging and Radiation Dose in Crohn's Disease[45]

S Patil, A Rustgi, F Vandermeer, R Cross

Diagnostic imaging is frequently used to aid in the management of CD; however, frequent diagnostic imaging can expose a patient to high doses of radiation over his or her lifetime. Optimal management of CD will result in clinical remission and decreased healthcare needs, including a decreased need for diagnostic imaging. In this study, Patil and colleagues investigated the ability of anti-TNF agents to decrease the need for diagnostic imaging in CD patients.

A total of 60 CD patients (mean age 34.3±11.0 years) who were initially treated with anti-TNF therapy and had at least 1 year of follow-up between 2004 and 2008 were included in this analysis. All radiation-based diagnostic imaging studies conducted in the 1 year prior to and 1 year after initiating anti-TNF treatment were counted.

The number of diagnostic imaging studies was significantly lower in the year following the initiation of anti-TNF therapy compared to the year prior to initiating therapy (4.0±7.9 vs 5.6±4.8; *P*=.0002). In the year following versus the year prior to initiating treatment, the number of computed tomography (CT) scans was 1.3±2.6 versus 3.2±2.8 (*P*<.0001), and the number of fluoroscopic examinations was 0.17±0.5 versus 0.48±0.8 (*P*=.01). In the year after initiating anti-TNF therapy, the overall radiation dose decreased by 17.6±25.4 mSv (*P*<.0001), and the radiation dose from CT scans decreased by 16.5±22.1 mSv (*P*<.0001). The greatest magnitude of radiation decrease was observed in patients with ileal and ileocolonic disease localization.

The authors concluded that the decrease in radiation dosage was largely due to a reduction in the number of CT scans performed. While the observed decrease in diagnostic imaging may be due to improvements in CD activity, the authors noted that these results could be biased, since patients preparing to begin anti-TNF therapy may be more likely to undergo extensive diagnostic evaluations.

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Commentary

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The study by Colombel and colleagues presented in this supplement was a secondary analysis of the EXTEND trial of adalimumab in CD. The EXTEND trial was primarily designed to examine endoscopic healing with adalimumab; this analysis determined the effect of disease duration on "deep remission" (defined as clinical remission plus endoscopic healing). A similar analysis in the CHARM trial of adalimumab in CD strongly suggested that patients with shorter durations of CD had higher clinical remission rates when treated with adalimumab. The present study showed that adalimumab maintenance therapy was associated with higher rates of deep remission at the end of 1 year compared to placebo maintenance therapy, and this effect was seen in all disease duration categories. Although a numerical trend for higher rates of deep remission was observed among patients with shorter durations of CD compared to those with longer disease durations, this trend did not quite meet statistical significance. However, this study was not powered for this particular endpoint, so the sample size may have been inadequate to detect statistical significance. Nevertheless, the results lend some support to the concept that certain endpoints, such as endoscopic healing, may be easier to achieve in patients with shorter disease durations, since these patients have had less opportunity to develop irreversible intestinal complications such as strictures, fistulas, or abscesses.

In another study, Reinisch and coworkers performed secondary analyses on data from an 8-week clinical trial of adalimumab for the induction of remission in moderately to severely active UC in order to determine the effect of adalimumab treatment on laboratory parameters in these patients. They found that adalimumab therapy was associated with significant improvements in hemoglobin levels, hematocrit fraction, red blood cell counts, serum total protein levels, serum albumin levels, and serum CRP levels, especially among patients treated with 160 mg adalimumab followed by 80 mg adalimumab. These secondary results add to the conclusion drawn from the primary endpoint of this trial—that treatment with adalimumab results in higher rates of clinical remission compared to placebo for patients with moderately to severely active UC.

A presentation by Sandborn and colleagues was a different secondary analysis of the same induction trial of adalimumab versus placebo for UC. The focus in this Sandborn study was on health-related QOL (HRQOL). Two validated survey instruments were employed at baseline and at Weeks 4 and 8 in all patients: the disease-specific IBDQ and the generic questionnaire SF-36. Mean IBDQ scores were significantly higher at Weeks 4 and 8 in patients treated with 160 mg adalimumab followed by 80 mg adalimumab than in those treated with placebo. When stratified by baseline CRP level, patients with elevated CRP levels had numerically higher IBDQ improvements at Week 4 than patients with normal CRP levels. Furthermore, having a body weight less than 70 kg was associated with more robust improvements in IBDQ scores at both Weeks 4 and 8. Mean SF-36 physical scores were significantly improved in patients who received 160 mg adalimumab followed by 80 mg adalimumab, and similar trends were seen for patients with elevated baseline CRP levels and patients with a body weight less than 70 kg. The HRQOL results are not surprising, as this improvement has been observed with other biologic agents, and we know that HRQOL is partly related to IBD disease activity. The weight-stratified analysis of these results is intriguing, however. Unlike infliximab, which is dosed according to body weight, doses of injectable anti-TNF agents have generally been fixed. It stands to reason that patients with a higher body weight might have a larger volume of distribution and therefore, potentially, a lower concentration of active drug. Of course, we should not compare across clinical trials, since different patients are enrolled in different studies, but I wonder if this finding explains why the remission rates observed in the adalimumab trial of UC are numerically lower than those seen in the ACT studies of infliximab for UC.

Hébuterne and colleagues studied HRQOL in patients enrolled in the MUSIC study, a trial that measured endoscopic improvement in patients treated with open-label certolizumab pegol for active CD. In this study, more than clinically meaningful improvements in IBDQ scores were observed at Weeks 10 and 54. This study also found that rates of IBDQ remission correlated with endoscopic remission as measured by CDEIS scores. These results again highlight the importance of reducing inflammation and inducing healing to improve IBD patients' HRQOL.

Lichtenstein and coworkers performed an interim analysis on data from the extension phase of the PRECiSE trials to estimate the long-term efficacy of certolizumab pegol in patients with CD. This analysis was performed

4.5 years after the initiation of the study, and it is important to note that 68% of patients were no longer being followed at this time. In the per-protocol analysis, clinical remission rates were still robust—in the mid-60% range—at 4.0–4.5 years; however, the fact that over two thirds of enrolled patients had been lost to follow-up limits the precision of this estimate.

Another induction trial of certolizumab pegol for moderately to severely active CD was presented by Sandborn and colleagues. This study missed its primary endpoint, clinical remission (CDAI <150 points) at Week 6 (31.6% certolizumab pegol vs 25.4% placebo; *P*=.17), but a secondary analysis stratified by baseline CRP level showed a significant difference in clinical remission rates in the 2 treatment arms among patients with baseline CRP levels at or above 5 mg/L. This finding brings to mind a similar phenomenon observed in a phase II trial of certolizumab pegol for CD that was published 5–6 years ago; in the PRECiSE 1 and 2 trials, baseline CRP level did not seem to be an important factor in predicting response. Is there something about the different mechanism of action of certolizumab pegol (eg, no apoptosis) that results in a different pattern of response with this drug? Time will tell. Since most of a patient's CDAI score is driven by symptoms, the CRP-specific result also highlights the importance of making major treatment decisions based on objective markers of inflammation and not relying solely on symptoms of abdominal pain, diarrhea, and fatigue.

Three retrospective, observational (ie, nonrandomized) studies detailing experience with infliximab are also highlighted in this supplement. Shafran and Burgunder describe potential predictors of response to infliximab among 125 CD patients. Primary nonresponse seemed to occur more often in patients with fibrostenotic CD, those with isolated small bowel disease, and active smokers. In a second study, Rostholder and colleagues noted an initial clinical response of 77% among 62 patients with UC who were treated with infliximab. At first glance, it might seem peculiar that patients with at least 2 years of colitis were less likely to progress to colectomy than those with shorter disease durations; however, several natural history studies of UC have demonstrated that the first year after diagnosis is associated with the highest colectomy rate. Finally, Tyagi and Cannon examined the utility of inpatient use of infliximab for UC and CD patients who were anti-TNF–naïve. The clinical response rate in this setting was quite high. The only note of caution I would introduce is that the decision to use infliximab in the acute setting may impact the type of surgery performed by our surgical colleagues, especially if colonic/pelvic surgery is involved. Some (but not all) surgical series indicate that the perioperative use of infliximab might increase the risk of early infectious complications after proctocolectomy, and colorectal surgeons at some centers will offer a 3-stage, rather than 2-stage, proctocolectomy with ileal pouch-anal anastomosis to such patients.

Harris and coworkers examined "gene chip" results from peripheral blood of confirmed IBD patients to identify genes that were accurate markers for the diagnosis of IBD. The authors found that a combination of 3 genes could achieve relatively high sensitivity and specificity for distinguishing between UC and CD. While intriguing, this work must be considered quite preliminary and needs to be confirmed by at least 1 other group of researchers, preferably in a cohort of patients with a range of diagnostic certainties, before such testing will have application in clinical practice.

In another study, Kotlyar and colleagues updated a meta-analysis of lymphoma risk among IBD patients receiving immunosuppressive medications. The results of 2 large, population-based studies were combined with results of 6 referral center–based studies to yield a pooled standardized incidence ratio (observed cases divided by expected cases) of approximately 4.5. Interestingly, there were no differences in the point estimates of relative risk when comparing the population-based studies with the referral center–based studies. Our message when counseling patients remains unchanged—while the relative risk of lymphoma is increased among IBD patients taking these medications relative to the general population, the absolute risk remains low.

Finally, Patil and colleagues examined the ability of anti-TNF therapy to decrease the need in CD patients for tests involving ionizing radiation. This study demonstrated significant reductions in the number of such tests in the year after anti-TNF therapy initiation compared to the year before this therapy was started. While this finding most likely reflects the ability of anti-TNF therapy to decrease bowel inflammation, symptoms, and possibly intestinal complications, we should not let such a result allow us to relax our vigilance in monitoring patients. The frequent disconnect between symptoms and objective inflammation, coupled with the often silent development of intestinal complications, results in the politically incorrect (but I think accurate) message that CD patients require frequent testing, especially before the treating clinician makes major treatment decisions.


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