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New Data on the Use of Biologic Agents for Crohn's Disease and Ulcerative Colitis: Highlights from the 2009 CCFA Advances in IBD Meeting

A Review of Selected Presentations from the 2009 Advances in Inflammatory Bowel Diseases/Crohn's & Colitis Foundation's Clinical and Research Conference
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Target Audience: This activity has been designed to meet the educational needs of gastroenterologists involved in the management of patients with inflammatory bowel disease.

Statement of Need/Program Overview: The abstract review monograph *New Data on the Use of Biologic Agents for Crohn's Disease and Ulcerative Colitis: Highlights from the 2009 CCFA Advances in IBD Meeting* will present the most current data updates emerging within this therapeutic area. The development and use of targeted biologic agents has demonstrated efficacy in inducing and maintaining remission in many patients with Crohn's disease. There is a clear educational need that exists in the gastroenterology community for an updated understanding of the appropriate use of biologic therapies, including the optimal timing of their use.

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

1. Review the current role of biologic therapies in the treatment of moderate-to-severe Crohn's disease.
2. Outline emerging data on the use of biologics as they relate to use in clinical practice.
3. Describe new strategies to maximize biologic efficacy and durability of response.

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Introduction

Crohn's Disease (CD) and ulcerative colitis (UC) are inflammatory bowel conditions characterized by abdominal pain, changes in bowel habits, and rectal bleeding. Whereas the inflammation associated with UC affects the mucosa only and is confined to the colon, CD is a transmural, potentially penetrating disease, which can manifest in discontinuous patches throughout the gastrointestinal tract.

Onset of CD occurs most commonly in people between the ages of 20 and 30, and prevalence estimates range from 26.0 to 198.5 cases per 100,000 persons in the United States.[1] Researchers have found evidence of a genetic predisposition for CD risk,[2] as well as an environmental component, as CD prevalence in western populations tends to be higher than in other areas of the world. Although the etiology of the disease is incompletely understood, the likely culprit of the inflammatory process is a dysregulation of the mucosal immune system in response to environmental triggers.

CD is a relapsing-remittent condition, with periods of active inflammation associated with significant morbidity and a decreased quality of life. The Crohn's Disease Activity Index (CDAI) is the primary tool used to assess the severity of CD in clinical trials. It takes clinical variables into account during the diagnosis and management of the disease. Although most cases of CD initially present with mild to moderately active disease, they will generally progress to moderately to severely active levels over time. As there is no cure for CD, the goal for treatment is to induce and maintain clinical and endoscopic remission and to avoid surgical intervention. Because of the chronic nature and unpredictable location of the disease, long-term medical management is required, and even surgical resection is not considered curative.

Until recently, the primary first-line treatment for CD was corticosteroids. Practice guidelines published by the American College of Gastroenterology (ACG) note that the usual course of therapy for moderate to severe CD is 40–60 mg of prednisone daily until the resolution of symptoms, which generally occurs between 7 and 28 days after the initiation of therapy.[3] This is typically followed by a taper of prednisone by 5 to 10 mg every 1 to 2 weeks; thus, the typical corticosteroid course is 2 to 3 months. However, the long-term use of steroids is not recommended, due to the high risk of steroid dependence, bone loss, and susceptibility to infections. Other options for maintenance therapy include the immunomodulators 6-mercaptopurine (6-MP), methotrexate, and azathioprine. Although they are effective, they carry risks of leukopenia, liver toxicity, and infection and other side effects.

The most promising recent development in the treatment of CD has been the introduction of biologic therapies. The majority of these agents target tumor necrosis factor (TNF), a cytokine produced by T lymphocytes and macrophages. TNF triggers a variety of proinflammatory cytokines in the mucosal immune system when activated. Infliximab, a partially humanized monoclonal antibody, was the first biologic agent approved for CD. It targets TNF-α and activated T lymphocytes to interrupt the inflammatory cycle of CD. It was followed more recently by the approval of adalimumab, a fully human anti-TNF monoclonal antibody that has shown efficacy in several trials, including CLASSIC I[4] and GAIN.[5] Certolizumab pegol, a pegylated Fab' fragment, also targets TNF-α, and has been evaluated in the PRECiSE 1 and PRECiSE 2 trials.[6,7] Natalizumab is a humanized monoclonal antibody that targets the cellular adhesion molecule α4-integrin. Although it has been shown to be effective in patients refractory to infliximab,[8] it carries an increased risk of progressive multifocal leukoencephalopathy. Vedolizumab is an investigational monoclonal antibody that is specific to the $\alpha_4\beta_7$ adhesion molecule. Researchers suggest that its specificity for this gastrointestinal target may lessen the risk of systemic infections. It is currently undergoing Phase III trials for UC and CD.[9]

In spite of promising clinical trial evidence and a growing body of real-world experience with biologic agents for CD treatment, several issues remain unresolved. Current research is examining optimal dosing strategies, long-term safety implications of biologics, and therapy choices for patients with severe, active disease. In December 2009, the Crohn's and Colitis Foundation held its National Clinical and Research Conference to share recent data. The following summaries highlight important new data that may begin to answer some of the questions surrounding the optimal use of biologic agents for these conditions.

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New Data on the Use of Biologic Agents for Crohn's Disease and Ulcerative Colitis: Highlights from the 2009 CCFA Advances in IBD Meeting

O-0003 Need for Rescue Therapy in IBD Patients on Infliximab Maintenance Therapy After Discontinuation of Immunomodulator

M Fischer, D Helper, M Chiorean, B Juliar

The use of immunosuppressant therapy in combination with anti-TNF agents in the treatment of CD has been a controversial issue. The ACG guidelines state that the use of infliximab combined with azathioprine is more effective than azathioprine alone in patients with moderate to severe CD, who have not responded to mesalamine or corticosteroids.[1] However, questions remain as to the safety of immunosuppression interruption in these patients[2] and the increased side effects that may occur with combination regimens.[3]

In an effort to determine the proportion of IBD patients requiring rescue therapy after de-escalation of immunomodulator therapy, Fischer and colleagues examined the records of patients in a single-center database.[4] The investigators identified patients on infliximab who had stopped immunomodulator therapy or decreased it by more than 50% in the absence of adverse events. Rescue therapy was defined as steroid use, biologic dose escalation or substitution, resumption of immunomodulator therapy, hospitalization, or surgery.

The researchers identified 321 patients receiving biologic therapy. Of these, 43 were in remission at the time of de-escalation. Forty patients had CD, whereas 3 had UC. Patients' mean age was 39.3, 39.5% were males, 93.0% were white, and 25.6% had a history of smoking. The median disease duration was 86.0 months, and 23.3% of patients had had previous surgery. The mean duration of remission on combination therapy prior to de-escalation was 20.2 months. Of all the patients with de-escalation of immunomodulator therapy, 22 patients (51.2%, all with CD) required rescue therapy during the 15.8 months of follow-up. Statistical analysis revealed that the only significant clinical risk factor for rescue therapy was ileocolonic, rather than ileal, disease location (odds ratio [OR]=15.4, 95% confidence interval [CI]=1.2-943.0, *P*=.03). The researchers found that other clinical variables, such as age, gender, age at diagnosis, disease duration and behavior, smoking, prior surgery, and the duration of combination therapy were not associated with the need for rescue therapy. The investigators concluded that a large proportion of patients require rescue therapy after discontinuing immunomodulator therapy, and that disease location is the only predictor associated with the need for rescue therapy.

P-0023 Long-term Follow-up of Patients Enrolled in the Randomized Controlled Trial of Infliximab for Prevention of Recurrent Crohn's Disease

S El-Hachem, M Regueiro, K Kevin, W Schraut, L Baidoo, J Harrison, M Pesci

In a trial that included 24 patients, Regueiro and colleagues[5] found that infliximab was more effective than placebo in preventing the recurrence of Crohn's disease 1 year after intestinal resective surgery. The investigators found a significantly lower rate of endoscopic recurrence in patients receiving infliximab (9.1%) than in those receiving a placebo (84.6%, *P*=.0006). They also found significantly lower rates for histologic recurrence (27.3% for infliximab vs. 84.6% for placebo, *P*=.01) and a nonsignificant increase in the rate of clinical remission (80.0% for infliximab vs. 53.8% for placebo, *P*=.38) In this long-term follow-up study, El-Hachem and associates provide 4-year data on remission and recurrence rates for this population.[6]

In the original trial, 13 patients were randomized to placebo and 11 to infliximab. At the completion of the trial, patients had a colonoscopy and were offered open-label infliximab. Another colonoscopy was performed between 6 and 12 months after the original trial, and yearly thereafter.

At the time of this analysis, 2, 3, and 4 year follow-up had been performed in 16, 6, and 2 patients, respectively. At the end of the original trial, 7 placebo patients opted for open-label infliximab therapy, and 5 were in remission at the 2-year follow-up point. In contrast, 3 infliximab

patients stopped therapy after the original trial, and all showed evidence of recurrence at the 2-year endoscopy. At year 3, one patient was switched from infliximab to adalimumab due to infusion reaction, and remained in remission. Among the 24 patients in the study, a total of 48 post-surgical endoscopic evaluations had been performed with the most recent treatment regimen classified as 25 (52%) anti-TNF (including infliximab or adalimumab), 18 (38%) no anti-TNF, and 5 (10%) partial anti-TNF, defined as prior anti-TNF therapy but not within 8 weeks of endoscopy. The researchers found that there was a strong gradient relationship between anti-TNF therapy and the rate of endoscopic remission and concluded that patients treated with post-surgical infliximab maintain remission with ongoing infusions, but relapse if infliximab is stopped. They also found that patients who did not receive anti-TNF agents may be successfully treated with infliximab if CD recurs after surgery.

P-0046 Stability of Infliximab Dosing in Crohn's Disease: Results from a Chart Review

H Waters, R McKenzie, O Lunacsek, M Franklin, B Lennert, C Piech

In order to assess the dose and frequency of infliximab maintenance treatment in patients with CD, Waters and associates, from Centocor, Inc., performed a retrospective medical record review at 7 community gastroenterology practices.[7] The investigators included patients who were at least 18 years of age with a diagnosis of CD and an infliximab index date (the date of first infliximab administration) occurring between the beginning of 2005 and the end of September 2007. Records were included from patients for whom at least 24 months of data were available, including a minimum of 12 months before and after the index date. Patients with evidence of biologic use in the 12 months prior to the index date, or who had participated in a clinical trial, were not included in the analysis. The researchers focused on maintenance therapy used after the initial 3 doses of infliximab.

A total of 182 patients were included in the analysis. The mean age of patients was 42 years, 47.3% were female, and the mean time from CD diagnosis to the first treatment with infliximab was 7.6 years. The mean patient weight was 81 kilograms. Of the 182 charts included, 37 (20%) had incomplete information regarding dose or frequency. Of the remaining 145 evaluable charts, 136 (94%) patients began maintenance therapy on 5 mg/kg, and of those, dosing and administration frequency was stable in 107 (79%) patients. The researchers found that increased dose or frequency was required for 15% of patients, whereas decreased frequency was seen in 4% of patients. Nine (6%) patients began maintenance therapy at higher infliximab doses. Of these, 6 remained stable, 2 experienced a decrease, and 1 experienced an increase in dosing. All 9 patients remained stable in their administration frequency.

The researchers concluded that over 90% of infliximab-treated CD patients received 5 mg/kg as the initial dose, and that the overwhelming majority of patients remained stable in their dosing. The investigators suggest that weight-based dosing allows providers to find the effective dose for each patient, which may remain relatively stable during the maintenance phase of the initial year of infliximab treatment.

P-0025 Emerging Safety Profile of Vedolizumab: A Novel, Selective Integrin Inhibitor for the Treatment of IBD

B Feagan, T Leach, C Milch, P Parikh, I Fox

Vedolizumab is a humanized version of Act-1, a monoclonal antibody to $\alpha_4\beta_7$ integrin.[8] Vedolizumab inhibits lymphocyte trafficking to gastrointestinal tissue by blocking $\alpha_4\beta_7$ adhesion to mucosal vascular addressin cell adhesion molecule (MAdCAM-1). Previous studies have shown that Act-1 has therapeutic activity for CD [9] and UC.[10] Because of its specificity for $\alpha_4\beta_7$ integrin,[11] vedolizumab has the potential for a lower risk of systemic opportunistic infections than that seen with nonspecific α_4 antagonists.

Feagan and colleagues presented safety findings from Phase I and II clinical trials of vedolizumab and its precursor, LDP-02.[12] They performed an integrated safety analysis on data from 9 clinical trials, 8 of which were placebo controlled. The studies enrolled a total of 579 participants, including healthy volunteers and patients with IBD. Of these subjects, 415 received vedolizumab or LDP-02 at single or multiple doses up to 10 mg/kg intravenously for up to 4 doses. In all, 248 (84%) drug-treated subjects reported at least one adverse event (AE), compared with 143 (87%) placebo subjects (Table 1).

The most common AEs among treated subjects were headache, nausea, exacerbation of UC, abdominal pain, fatigue and nasopharyngitis. The researchers found similar rates of serious adverse events among treatment groups: 12% in the drug-treated group versus 14% in the placebo group. Of the drug-treated subjects, 135 (33%) experienced at least one infection, compared with 37 (23%) placebo subjects. The upper respiratory tract was the most common infection site reported by all groups. Herpes labialis was reported by 11 (2.3%) treated subjects versus 1 (0.6%) placebo subject, and the rates of mucosal

Table 1. Vedolizumab Safety Summary from Completed Studies

Event	Placebo, n (%) n=164	Vedolizumab, n (%)			
		Low dose n=180	Mid dose n=168	High dose n=67	Combined n=415
Any AE	143 (87)	152 (84)	147 (88)	49 (73)	348 (84)
Severe AE	38 (23)	37 (21)	45 (27)	5 (7)	87 (21)
Drug-related AE	55 (34)	70 (39)	56 (33)	22 (33)	148 (36)
AE resulting in discontinuation	15 (9)	13 (7)	12 (7)	0	25 (6)
SAE	23 (14)	21 (12)	27 (16)	2 (3)	50 (12)
Drug-related SAE	2 (1)	4 (2)	0	0	4 (<1)
SAE resulting in discontinuation	5 (3)	5 (3)	5 (3)	0	10 (2)
On-study deaths	0	0	0	0	0

Low dose=0.15, 0.2, 0.5 mg/kg; Mid dose=1.5, 2.0, 2.5 mg/kg; High dose=6.0, 10.0 mg/kg.

Data from Feagan et al.[12]

candidiasis were 1.2% and 0% in the treated and placebo groups, respectively. The rates of gastrointestinal infections were similar for both groups, at 1% or lower overall. Serious infections were experienced by 1.4% of drug-treated subjects compared with 1.8% of placebo subjects.

The investigators noted that no opportunistic infections were reported during any clinical trial of vedolizumab or LDP-02. One patient with UC, who received one dose of the drug, developed a primary cytomegalovirus infection 21 days later, which resolved without antiviral therapy. The investigators reported that vedolizumab was not associated with lymphocytosis or other increases in white blood cell counts, liver function abnormalities, progressive multifocal leukoencephalopathy, or JC viremia.

Feagan and associates concluded that vedolizumab has been well-tolerated, with no increase in systemic infections but a possible trend in increased upper respiratory and mucosal infections. They suggest that these data, combined with the absence of lymphocytosis, are consistent with the specificity of vedolizumab and the distribution of MAdCAM-1 in mucosal tissue. The researchers found that the selectivity of vedolizumab for $\alpha_4\beta_7$ integrin—and the specificity of $\alpha_4\beta_7$ integrin for local immunomodulation within the GI tract—offers less risk for systemic side effects than those incurred by less specific agents. Ongoing Phase III trials under the manufacturer's GEMINI program will further study the effects of vedolizumab in IBD patients.[13]

P-0028 Sustained Mucosal Healing in Adalimumab-Treated Patients with Moderate to Severe Ileocolonic Crohn's Disease: Results of the EXTEND Trial

P Rutgeerts, G D'Haens, G van Assche, W Sandborn, D Wolf, J Colombel, W Reinisch, K Geboes, M Khan, A Lazar, A Camez, P Pollack

In the open-label EXTEND trial, Rutgeerts and colleagues found that induction plus maintenance therapy with adalimumab was better than induction therapy alone in maintaining remission in patients with moderate-to-severe ileocolonic CD.[14] After 52 weeks, 24% of adalimumab patients had maintained mucosal healing, compared with none of the placebo patients. In this analysis, Rutgeerts and colleagues present additional data on the safety and efficacy of adalimumab for mucosal healing.[15]

EXTEND enrolled patients with moderate to severe ileocolonic CD (defined as a Crohn's Disease Activity Index [CDAI] score between 220 and 450) and baseline mucosal ulceration (defined as a Simple Endoscopic Score for Crohn's Disease [SES-CD] of 2 or 3 on one or more colon segments). All patients received open-label adalimumab induction therapy of 160 mg at week 0 and 80 mg at week 2. At week 4, patients were randomized

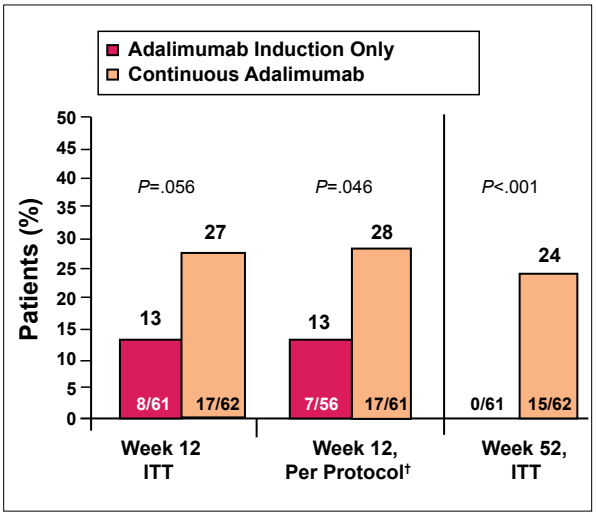

Figure 1. Complete mucosal healing at weeks 12 and 52 in the EXTEND Trial: NRI analysis.*

ITT=intention to treat; NRI=nonresponder imputation.

*NRI for missing ulceration at weeks 12 and 52 and for missing ulceration assessment of switched patients at week 52.

†Per protocol represents all ITT patients who did not have a significant protocol deviation.

to receive maintenance therapy with adalimumab 40 mg every other week or placebo through week 52. Beginning in week 8, patients with flares or nonresponse could receive open-label adalimumab every other week, or every week in the case of continued flares or nonresponse. Patients underwent colonoscopy at baseline, at week 12 (or during unscheduled visits for patients who switched to open-label therapy before week 12), at time of switch if after week 12, and at week 52 (or at the time of early termination). The primary endpoint was complete mucosal healing as determined by the review committee's visual assessment of week-12 endoscopies. The secondary endpoints included clinical remission (defined as a CDAI score of <150); Crohn's Disease Endoscopic Index of Severity (CDEIS) remission (defined as a score of ≤4), and mean change in SES-CD at weeks 12 and 52.

Of the 135 patients enrolled in the EXTEND trial, 129 were randomized. At baseline, patients' mean CDAI was 320, mean CDEIS score was 19, and the mean duration of CD was 10 years. Sixty-one percent of patients had had prior anti-TNF exposure. Concomitant medications included steroids for 26% of patients and immunosuppressants for 41%. At week 12, complete mucosal healing for the intent-to-treat population was 27.4% for the group receiving continuous adalimumab and 13.1% for the induction-only group. At week 52, the rates of complete mucosal healing were 24.2% and 0%, respectively (Figure 1). The mean SES-CD change was 11.582 for the continuous adalimumab group versus 6.408 for the induction-only group (P<.001). At week 52, 9.2% of induction-only patients were in clinical remission, compared with 32.8% of the continuous adalimumab patients. The researchers found no differences in the frequency of serious adverse events per 100 patient-years between the 2 groups.

The investigators concluded that adalimumab maintenance therapy was effective in healing the intestinal mucosa of patients with moderate to severe ileocolonic CD. They suggest that the residual effects of the induction regimen may explain the high rate of healing among induction-only patients at week 12. The researchers found that mucosal healing was sustained for 1 year, as confirmed by CDEIS and SES-CD scores.

P-0059 Patterns and Predictors of Dosage Increase in Patients Treated with Adalimumab for Crohn's Disease in the United States

E Loftus Jr, X Pan, P Zurawski, J Chao, P Mulani

The CLASSIC I[16] and GAIN[17] trials showed adalimumab to be an effective therapy for inducing and maintaining CD remission. After induction therapy, adalimumab is usually dosed at 40 mg every other week for maintenance therapy. In a recent clinical trial, 27% of patients increased their dosage to a weekly schedule within 1 year.[18] In the current study, Loftus and colleagues from the Mayo Clinic and Abbott Laboratories analyzed data from a large specialty pharmacy-dispensing database to determine dosage patterns and predictors for dosage increase in the clinical practice setting.[19]

The researchers included the records of CD patients whose first dose of adalimumab was on or after March 1, 2007, and followed them from March 2007 to July 2008. Maintenance therapy was defined as at least 3 dispensing events of adalimumab within one year, and a weekly dosage regimen was defined as at least 2 consecutive weekly doses after the first dispensing event. The investigators used a Cox proportional regression model to examine the impact of age, sex, geographic region, and use of a 160/80 mg induction regimen on the weekly dosage rate.

Of the 1,335 patients included in this analysis, 151 (11.3%) had weekly dosing at any time during the study period. The 12-month cumulative risk of weekly dosing was 15.5%. Geographic region and not starting on a 160/80 mg induction dose were significant predictors for weekly adalimumab use. Patients who received 160/80 mg as induction therapy were approximately half as likely to receive weekly dosing as those who did not

start with this regimen. The western and southern regions of the United States had significantly lower rates of weekly dosing than did the northeastern region. The researchers concluded that the rate of weekly maintenance dosing in a real-world setting was much lower than that observed in clinical trials, and that patients who received 160/80 mg induction therapy were significantly less likely to receive weekly dosing.

P-0122 Adalimumab Therapy Maintains Steroid-free Remission and Fistula Closure in Patients with Moderate to Severe Crohn's Disease: Results of an Open-Label Study in Canada (ACCESS)

R Panaccione, E Loftus Jr, D Binion, K McHugh, N Chen, J Chao, P Mulani

In another study of adalimumab, Panaccione and associates from the University of Calgary, the University of Pittsburgh, the Mayo Clinic, and Abbott Laboratories evaluated adalimumab's ability to induce and maintain steroid-free remission and fistula closure in a Canadian open-label, multicenter trial of 304 patients with moderately or severely active CD.[20]

This study enrolled patients who had failed infliximab therapy as well as those who were naïve to biologic therapy. Patients received induction therapy of 160 mg and 80 mg of adalimumab at weeks 0 and 2, respectively, followed by a maintenance regimen of 40 mg every other week. In the case of flares or nonresponse, regimens were changed to 40 mg weekly starting at week 8. The endpoints included steroid-free remission (defined as Harvey-Bradshaw Index [HBI] ≤4 and steroid-free), sustained steroid-free remission (defined as remission and freedom from steroids for at least 90 days), and complete fistula closure (defined as closure of all fistulas that were draining at baseline).

At baseline, 144 patients were receiving steroids and 68 patients had at least 1 draining fistula. At 24 weeks, the rates of steroid-free remission and sustained steroid-free remission for infliximab-experienced patients were 31% and 20% respectively, according to a nonresponder imputation analysis. For infliximab-naïve patients, the rates were 38% and 27%, respectively. The rates of fistula closure at 12 weeks were 26% for infliximab-experienced patients and 48% for infliximab-naïve patients. At 24 weeks, these rates were 28% and 60%, respectively (Figure 2). The researchers concluded that adalimumab was effective in inducing and maintaining steroid-free remission and closing fistulas in both infliximab-naïve patients and those with a history of infliximab use.

P-0034 Rapid Improvement of Patient-reported CDAI Diary Components by Day 8 in Active Crohn's Disease Patients Treated with Certolizumab Pegol

S Schreiber, M Khaliq-Kareemi, I Lawrance, O Thomsen, R Bloomfield, W Sandborn

The PRECiSE I Study found that certolizumab pegol (CZP) provided a modest improvement in response rates compared with placebo in patients with moderate-to-severe CD.[21] In PRECiSE 2, the researchers found that responders to 6-week induction doses of CZP who received maintenance CZP therapy were more likely to maintain remission at 26 weeks than those who were switched to placebo.[22] In this analysis of PRECiSE 2, Schreiber and colleagues sought to determine the onset

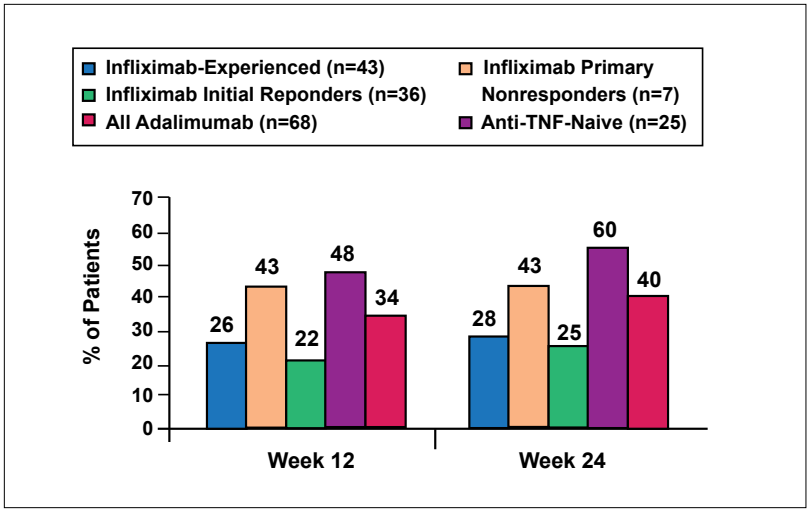

Figure 2. Complete closure of baseline fistulas in the ACCESS Trial: NRI analysis.

NRI=nonresponder imputation

of action of CZP by assessing the patient-reported diary components of the CD Activity Index (CDAI).[23]

Patients with active CD (defined as a CDAI score of 220-450) had open-label induction with CZP at weeks 0, 2, and 4. The CDAI was used to determine response, which was defined as a reduction in CDAI of at least 100 points from week 0. The investigators performed post-hoc analyses of the 3 patient-reported CDAI components of the diary cards, which included information on the number of loose or liquid stools per day, abdominal pain, and general well-being. The researchers compared findings for responders and nonresponders through day 8 of treatment.

Of the 668 patients on induction therapy, 428 (64%) responded at week 6 and received double-blinded maintenance therapy, whereas 240 (36%) did not respond and thus discontinued treatment. At baseline, the mean number of loose or liquid stools was similar among responders and nonresponders (4.9 and 5.1, respectively). By day 8, the mean number of stools per day had decreased by 1.5 in the responders and by 0.7 in the nonresponders. At baseline, the majority of responders and nonresponders rated their abdominal pain as moderate and their general well-being as poor. By day 8, there was a statistically significant difference between the patient-reported scores for abdominal pain (P=.002) and general well being (P=.001). In the responders and nonresponders with severe abdominal pain and a reported terrible general well being at baseline, 17.6% and 11.5% rated no pain by day 8, and 16.7% and 9.5% rated themselves as generally well by day 8. The researchers concluded that CZP rapidly improved symptoms in patients with active CD.

P-0068 Natalizumab Reduces the Rate of Hospitalization in Moderate to Severe Crohn's Patients: Evidence from the Clinical Trial Program

B Sands, C Siegel, W Sandborn, B Feagan, S Hass, A Nag, T Niecko

The ENCORE trial showed natalizumab to be effective in patients with moderate to severe CD who are refractory to TNF inhibitors and other CD therapies.[24] ENACT-1 and ENACT-2 were induction and maintenance studies that found small, nonsignificant improvements in response and remission rates with natalizumab versus placebo, and ENCORE was an open-label extension study. [25] In this analysis, Sands and colleagues from the Massachusetts General Hospital and other centers including Elan Pharmaceuticals, evaluated the effect of natalizumab on hospitalization rates during the induction and maintenance phases of therapy, using data from these trials.[26] The researchers identified hospitalizations from adverse event reports and determined the rates of all-cause hospitalization and CD-related hospitalization per 100 patients over the 84-day induction period and the 336-day maintenance period.

During induction therapy, the all-cause hospitalization rate was 11.2 per 100 patients for placebo, compared with 7.3 for the natalizumab cohort (P=.02). During the 48-week maintenance period, the rate was 21.3 for placebo, compared with 12.0 for natalizumab patients (P=.04). When the investigators restricted the sample to patients with prior exposure to anti-TNF therapy, there was a larger difference between treated and untreated patients: for the induction period, the rates were 21.5/100 patients on placebo and 9.4/100 patients on natalizumab (P<.01). For the maintenance populations, the rates were 21.5/100 patients for placebo and 9.4/100 patients for natalizumab (P=.03).

An analysis of CD-related hospitalization yielded similar results. In the overall sample, the rates were 8.3/100 patients for placebo and 5.7/100 patients for natalizumab (P=.07) during the induction period and 13.9/100 and 5.8/100 (P=.03) for the same groups during the maintenance period. In the subset of patients who had previously received anti-TNF therapy, treatment was associated with a relative risk reduction in hospitalization for both induction and maintenance therapy of more than 50%. The low number of surgeries hampered the evaluation of surgery rates. In the subgroup of patients with a history of anti-TNF therapy, there was no difference in surgery rates during induction, and a statistically nonsignificant 55% reduction in surgeries during maintenance (P=.22).

The investigators concluded that treatment with natalizumab was associated with significant and clinically meaningful reductions in the rate of all-cause and CD-related hospitalizations. For patients who had previously received anti-TNF therapy (the approved patient population for natalizumab), the rates of both types of hospitalizations were also markedly lower in natalizumab-treated patients than in those who had received placebo. Within the 48-week maintenance period, natalizumab was associated with a 75% reduction in the incidence of CD-related hospitalization.

P-0123 Outcomes of Salvage Therapy for Acute Severe Ulcerative Colitis: Cyclosporine Versus Infliximab

G Radford-Smith, A Croft, J Doecke, A Walsh

Acute severe UC (ASUC) is a common and serious complication of UC. It is defined by the Truelove and Witts criteria as the presence of six or more stools per day, with any of the following conditions: a body temperature of more than 37.8°C; a pulse rate of more than 90 bpm; a hemoglobin level of less than 10.5 g/dL,

or an erythrocyte sedimentation rate (ESR) of more than 30 mm/h.[27] Although there is a lack of clinical trial data to strongly support it, current medical practice for ASUC includes the use of cyclosporine or infliximab. In this analysis, Radford-Smith and colleagues compared outcomes of cyclosporine and infliximab in a prospective study of steroid-refractory ASUC patients.[28] Seventy-two consecutive ASUC presentations that met the Truelove and Witts criteria at an Australian medical center between 1996 and 2009 were evaluated, representing a total of 68 patients. The endpoints included in the study were clinical outcomes at discharge and at 12 months post-discharge, specifically evaluating whether the cases resulted in total colectomy or medical management after discharge.

Of the 72 total cases of ASUC, 44 (61%) were treated with cyclosporine and 28 (39%) were treated with infliximab. Among cases treated with cyclosporine, 23 (52%) proceeded to total colectomy before discharge, compared with 5 (18%) of the infliximab-treated patients, a difference that was found to be statistically significant (*P*=.003). At the 12-month follow-up point, 30 (68%) cyclosporine cases and 11 (44%) infliximab cases had required surgery for recurrent severe disease (*P*=.049).

The investigators concluded that the longitudinal outcomes data from this series of patients suggest that infliximab is more effective than cyclosporine in preventing the need for surgery in the short term. However, they believe that a randomized controlled trial would provide more definitive proof of the benefit of infliximab in the ASUC population.

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Commentary

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When interpreting retrospective studies, it is important to remember that there are inevitable confounding biases that may be difficult to observe. In the study by Fisher and colleagues of patients receiving combination biologic and immunomodulator therapy, approximately half of the subset of patients who underwent de-escalation of immunomodulators required rescue therapy over the following 15 months. In order to verify these results, it would be interesting to look at all of their patients in a multivariable model, to see if the process of de-escalation was an independent risk factor for requiring rescue therapy. It is not clear if the regression analysis used by the authors looked at each factor univariately or if a multivariable model was used. This does, however, add to the growing evidence that the benefits of combination therapy likely outweigh our concerns regarding increased toxicity. These data also suggest that patients with ileocolonic disease are at higher risk for requiring rescue therapy and should be de-escalated off of immunomodulators with the most caution. Again, patients with ileocolonic disease are the most likely to experience recurrence, as it tends to be more aggressive than strictly ileal or colonic manifestations. In addition, patients receiving any type of internal, primary anastomosis, which does not include an ostomy, have free reflux of colonic content into the small bowel. This is more likely to stimulate gut immunity and cause a recurrence, as opposed to an ileostomy, where there is considerably less bacterial stimulation.

El-Hachem and colleagues provide follow-up from a study of infliximab use in the post-operative setting. This is a small trial where a few patients were followed out to 4 years but most were followed for 2 years. The investigators show that patients who received placebo in the blinded portion of the study and opted for open-label infliximab received benefit in that they were less likely to recur. In contrast, the group who started on infliximab but then stopped therapy, all experienced endoscopic disease recurrence. This indicates that the strategy of post-operative anti-TNF therapy in patients at high risk for recurrence will work but requires the administration of therapy for more than one year.

Waters and colleagues looked at a group of 180 patients with 12 months of follow-up, both before and after starting on infliximab, to gauge the need for dose escalation. They found that dosing, in the short term out to 1 year, was relatively stable and escalation was only necessary in approximately 20% of patients. It should be noted that this real-world observation cannot be compared to the stringent data from clinical trials of this or other biologics, where higher rates of dose escalation are seen, in order to meet strict endpoints of response and remission. The loss of 20% of study patients due to incomplete medical record documentation limits the certainty of these results. Another caveat stems from the follow-up of only 1 year. It would be interesting to continue following these patients and see if escalation was required 5 years from now.

Feagan and colleagues report on the safety of vedolizumab, an experimental biologic agent with promising efficacy data. Given its molecular similarity to natalizumab, establishment of its safety is a primary concern. Current data indicate that the target of vedolizumab, the integrin subunit $\alpha_4\beta_7$, is specific to the gut, and has no expression elsewhere in the body. As a gut-specific agent, it should carry no risk of neurologic complication such as progressive multifocal leukoencephalopathy (PML).

In the current pooled analysis, 570 patients receiving at least one dose of vedolizumab were examined for adverse events. Thus far, there have been no worrisome signals beyond the rise in infections that is seen with all biologics. Regardless, it remains early in the history of the drug. With natalizumab, there were 3,000 patients treated before the first PML cases were described and vedolizumab patients have not yet been observed for nearly as long.

The results of the EXTEND trial by Rutgeerts and colleagues are slightly disappointing in that the investigators missed detection of a statistically significant difference in the primary endpoint by a single patient. Nonetheless, the overall findings of the study support a role for adalimumab in the achievement of mucosal healing. In this trial, both the active-treatment and the placebo groups received two doses of open-label adalimumab.

This likely resulted in a carry-over effect where some of those placebo patients showed healing at week 12. Had the investigators compared a true placebo group that received no drug, they might have seen a significant difference between the treatment and placebo arms. In any case, when comparing endoscopic healing rates at 52 weeks, there is a huge difference in the intention-to-treat analysis, suggesting efficacy for adalimumuab in terms of mucosal healing. Mucosal healing can be seen as an important intermediate endpoint, as the prevention of ulceration suggests the prevention of transmural inflammation, less stricturing, less fistula, and, over time, less hospitalization and surgery.

Our study of adalimumab utilized a specialty pharmacy database to track a group of patients who went from every other week to weekly dosing. The overall 12-month likelihood of escalation was 15% and the biggest predictor of the need for weekly dosing was geographic region. Patients in the Northeast had the highest rate of dose escalation. Another interesting predictive factor was the intensity of the induction regimen. Patients who received 80 mg and 40 mg as induction doses, or who started at 40 mg from the beginning, were more likely to require eventual escalation than those receiving the higher initial doses of 160 mg followed by 80 mg. This provides circumstantial evidence that induction dosing is important in getting patients started on effective therapy.

The greatest caveat to these findings is that many insurance companies initially denied any request for adalimumab dose escalation, because it was not in the original labelling for the drug. This may be reflected in the current analysis as a lack of need for escalation. Therefore, 15% represents a minimum and the real need for dose escalation is likely somewhat higher.

In real-world practice, secondary endpoints like steroid use and fistulization are important to examine in subsets of patients who are difficult to treat. The study headed by Dr. Panaccione was a Canadian open-label study of initial clinical experience with adalimumab, which was designed to develop a sense of how the drug worked in clinical practice. Some of the patients were infliximab failures and others were biologic-naive. This study illustrates that adalimumab can effectively control fistula and allow for steroid cessation, in both infliximab-experienced and biologic-naive patients, and that adalimumab is a reasonable choice as either a first-line or second-line anti-TNF.

Schreiber and colleagues, in their subanalysis of PRECISE 2, considered the onset of action of our third anti-TNF choice, certolizumab pegol. These patients received induction doses at weeks 0, 2, and 4 and were assessed at week 6. However, as part of the trial, all patients had CDAI scores recorded at regular intervals and the investigators went back to the primary trial data and looked at the drop in CDAI score as patients started on open-label therapy. The investigators found that by day 8, a statistically significant divergence in stool frequency, abdominal pain, and general well-being could be seen between placebo and certolizumab patients. Whether this is clinically significant remains unclear. Although 8 days may represent an average, some patients may not respond until day 14 or even day 21 and a lack of response at day 8 cannot be interpreted as a treatment failure. Regardless, it remains encouraging to see not just a biologic effect but a clinical effect, in some patients, so early in the treatment course.

Sands and colleagues performed a meta-analysis of the natalizumab clinical trials program in CD and considered hospitalization rates to see the differences between placebo and natalizumab patients. When looking at all-cause hospitalization and comparing natalizumab to placebo, the natalizumab patients had a rate of hospitalization that was 35% to 45% lower than that of placebo patients, and rates among the subset of patients previously exposed to anti-TNF therapy were reduced even further. Similar reductions were seen for Crohn's-related hospitalizations, both in the overall groups and in those previously exposed to anti-TNF therapy. This shows that natalizumab, beyond controlling symptoms, can affect longer term outcomes of hospitalization and possibly surgery.

Finally, Radford-Smith and colleagues followed patients with severe ulcerative colitis, who had failed intravenous steroids and were treated with either cyclosporine or infliximab. They found that half of cyclosporine-treated patients required colectomy before release from the hospital. Those who received infliximab had a significantly lower colectomy rate of 18%. At 12 months of follow-up, the surgery rates were still higher in the cyclosporine group, suggesting that infliximab may be more effective than cyclosporine in both the acute and maintenance settings of acute severe colitis. However, this was a nonrandomized observational study, and definitive conclusions cannot be drawn until a head-to-head trial is performed.

Suggested Reading

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Cho SM, Cho SW, Regueiro M. Postoperative management of Crohn's disease. *Med Clin North Am.* 2010;94:1-18.

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New Data on the Use of Biologic Agents for Crohn's Disease and Ulcerative Colitis: Highlights from the 2009 CCFA Advances in IBD Meeting

CME Post-Test: Circle the correct answer for each question below.

1. In a study of rescue therapy performed by Fischer and colleagues, examining the need for rescue therapy after de-escalation of immunomodulator therapy in Crohn's disease, the only significant clinical risk factor for rescue therapy was:

   a. Ileocolonic disease location
   b. Ileal disease location
   c. Age at diagnosis
   d. Length of disease history

2. True or false? In a long-term follow-up study performed by El-Hachem and associates, a strong inverse relationship was discovered between anti-TNF therapy and the rate of endoscopic remission.

   a. True
   b. False

3. In the integrated safety analysis of vedolizumab performed by Feagan and colleagues, what was the most common type of infection experienced by drug-treated patients?

   a. Gastrointestinal infections
   b. Upper respiratory tract infections
   c. Herpes labialis
   d. Systemic opportunistic infections

4. A chart review performed by Waters and associates found that ___% of CD patients increased their maintenance dose or dose frequency of infliximab during the study period.

   a. 10
   b. 30
   c. 15
   d. 25

5. True or false? The EXTEND trial showed a statistically nonsignificant increase in the proportion of patients in remission on continuous adalimumab therapy versus induction-only therapy.

   a. True
   b. False

6. In the study of prescribing patterns by Loftus and colleagues, what was the 12-month cumulative rate of weekly dosing?

   a. 15.5%
   b. 20.5%
   c. 10.5%
   d. 25.5%

7. The ACCESS study evaluated the efficacy of what biologic agent?

   a. Certolizumab pegol
   b. Infliximab
   c. Adalimumab
   d. Natalizumab

8. The study of onset of action for certolizumab pegol by Schrieber and colleagues assessed the onset of action for symptom relief through day __.

   a. 10
   b. 5
   c. 14
   d. 8

9. True or false? A study by Sands and associates found that, within a 48-week maintenance period, natalizumab was associated with a significant reduction in the incidence of CD-related hospitalization.

   a. True
   b. False

10. In a study of salvage therapy for acute severe ulcerative colitis, 52% of cyclosporine-treated cases proceeded to total colectomy before discharge, compared with ___ of infliximab-treated patients.

    a. 18%
    b. 57%
    c. 13%
    d. 23%

Evaluation Form New Data on the Use of Biologic Agents for Crohn's Disease and Ulcerative Colitis: Highlights from the 2009 CCFA Advances in IBD Meeting

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Learning Objectives
After participating this activity, I am now better able to:

1. Review the current role of biologic therapies in the treatment of moderate-to-severe Crohn's disease.	1 2 3 4 5
2. Outline emerging data on the use of biologics as they relate to use in clinical practice.	1 2 3 4 5
3. Describe new strategies to maximize biologic efficacy and durability of response.	1 2 3 4 5

Based upon your participation in this activity, choose the statement(s) that apply:
❒ I gained new strategies/skills/information that I can apply to my area of practice.
❒ I plan to implement new strategies/skills/information into my practice.

What strategies/changes do you plan to implement into your practice? _____

What barriers do you see to making a change in your practice? _____

Which of the following best describes the impact of this activity on your performance?
❒ I will implement the information in my area of practice.
❒ I need more information before I can change my practice behavior.
❒ This activity will not change my practice, as my current practice is consistent with the information presented.
❒ This activity will not change my practice, as I do not agree with the information presented.

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree
The content presented:

Enhanced my current knowledge base	1 2 3 4 5
Addressed my most pressing questions	1 2 3 4 5
Promoted improvements or quality in health care	1 2 3 4 5
Was scientifically rigorous and evidence-based	1 2 3 4 5
Avoided commercial bias or influence	1 2 3 4 5

Would you be willing to participate in a post-activity follow-up survey? ❒ Yes ❒ No

Please list any topics you would like to see addressed in future educational activities: _____

If you wish to receive acknowledgment for completing for this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

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