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Updates in the Diagnosis and Treatment of Inflammatory Bowel Disease: Highlights From Digestive Disease Week 2011

A Review of Selected Presentations From
Digestive Disease Week 2011
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With commentary by:

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Target Audience: This activity has been designed to meet the educational needs of gastroenterologists who treat patients with Crohn's disease (CD) and/or ulcerative colitis (UC).

Statement of Need/Program Overview: Various abstracts were presented at Digestive Disease Week 2011. Unfortunately, physicians cannot attend all of the poster sessions in their therapeutic area, and some physicians may have been unable to attend this meeting. Summaries of selected abstracts from this conference will provide reader-friendly synopses of new clinical data, present new analyses regarding the incidence of side effects associated with certain medications, and review the most recent findings of new agents and already approved agents in new settings. An expert commentary following these summaries will help readers place this new information into context and discuss how these new data impact clinical practice.

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: Gary R. Lichtenstein, MD, is Director of the Inflammatory Bowel Disease Program and Professor of Medicine at the University of Pennsylvania in Philadelphia, Pennsylvania.

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Highlights From Digestive Disease Week 2011

Predictors of a 15-Year Non-Severe Course in Crohn's Disease[1]

J Cosnes, I Nion-Larmurier, A Bourrier, H Sokol, F Roux, F Mistretta, L Beaugerie, P Seksik

Crohn's disease (CD) is a lifelong disease, with most patients experiencing a chronic, intermittent disease course.[2] The natural history of the disease varies, however, with about 13% of patients experiencing an unremitting disease course and 10% of patients achieving prolonged remission; moreover, as many as 57% of patients will need at least 1 surgical resection.[2]

The aim of this large, prospective study of 600 CD patients was to determine which factors predict a nonsevere disease course. Patients were followed from 1995 to 2009. This study included 244 men and 356 women; patients' median age in 1995 was 32.6 years (interquartile range [IQR], 26.2–42.5 years). Median disease duration prior to 1995 was 7 years (IQR, 2.9–12.4 years). Other information collected in 1995 included family history of inflammatory bowel disease (IBD); patients' educational level; and disease characteristics, including duration, systemic manifestations, disease location and behavior according to the Montreal classification system, rectal involvement, perianal disease, prior surgery, and need for immunosuppressant therapy.

Prospectively collected data included annual disease activity, therapies, surgical interventions, and disease complications. Disease was considered to be severe if the patient experienced active disease for more than 3 of 12 years, if more than 1 intestinal resection or a permanent stoma was required during the course of the 15-year study, or if the disease led to death. All other cases were considered to be nonsevere. Predictors of nonsevere disease were identified using univariate and multivariate logistic regression models.

Overall, 279 patients had a 15-year, nonsevere disease course. Among these patients, 61 had undergone surgery once, 62 had experienced 1 year with a flare, 128 had experienced 2–3 years with a flare, and 6 died from unrelated causes. One hundred and sixteen patients who had nonsevere disease eventually received immunosuppressants, and 14 patients with nonsevere disease received biologic agents; in patients with severe disease, immunosuppressants and biologic agents were used by 268 patients and 97 patients, respectively.

After adjusting for confounding factors, predictive factors that were significantly associated with a 15-year, nonsevere disease course included being a nonsmoker (OR [odds ratio], 1.49; 95% confidence interval [CI], 1.06–2.08); having rectal-sparing disease (OR, 1.56; 95% CI, 1.11–2.22); having a higher educational level (OR, 1.48; 95% CI, 1.05–2.09); older age (OR per 1 year, 1.01; 95% CI, 1.00–1.03); and longer disease duration prior to study inclusion (OR per 1 year, 1.05; 95% CI, 1.02–1.08).

Rectal involvement was the only disease characteristic related to long-term prognosis of CD. Patient characteristics associated with a more severe disease course included smoking and lower educational level, both of which may have a negative effect on patients' compliance with therapy. Older age and longer disease duration were both associated with a less severe disease course.

Fecal Calprotectin Is Strongly Predictive of Clinical Disease Activity and Histological Severity in Inflammatory Bowel Disease[3]

G Chung-Faye, K Sandhu, RP Logan, RA Sherwood

Although fecal calprotectin (FC) is a noninvasive surrogate marker of intestinal inflammation that holds promise as a diagnostic tool, its predictive role with regard to clinical and histologic activity of IBD is uncertain. To establish the value of FC in the assessment of clinical disease and histologic severity in IBD, 112 patients with ulcerative colitis (UC) and 45 patients with CD were evaluated via colonoscopy with biopsy. FC levels were measured in all patients, and Mayo clinical response scores were obtained for UC patients. All patients were graded using a simplified histology grading system in which scores ranged from normal (0) to mild (1), moderate (2), or severe (3).

Statistical analyses showed that UC patients with normal or mild (grade 0–1) histology had a significantly lower mean FC level than patients with moderate or severe (grade 2–3) histology (238 µg/g vs 1,752 µg/g; $P<.0001$). FC level was also strongly correlated with

Mayo scores (Spearman's correlation coefficient=0.752; *P*<.001) and histology scores (Spearman's correlation coefficient=0.621; *P*<.001).

CD patients with normal or mild histology scores also had a significantly lower mean FC level than CD patients with moderate or severe histology scores (119 µg/g vs 1,740 µg/g; *P*=.004). Again, statistical analysis found a strong correlation between FC levels and histology scores in CD patients (Spearman's correlation coefficient=0.757; *P*<.001).

Receiver operating characteristic (ROC) analyses for UC patients indicated an area under the curve (AUC) of 0.88; with a cutoff FC value of 240 µg/g, FC testing yielded an 83% sensitivity and 74% specificity for detecting moderate or severe disease. For CD patients, ROC analyses led to an AUC of 0.97 and a cutoff FC value of 218 µg/g; this cutoff value yielded a 91% sensitivity and 85% specificity for detecting moderate or severe disease.

Based on the strong correlation between FC and histology scores, high FC levels appear to be strongly predictive of histologically active disease. These findings highlight the utility of FC as a valuable, noninvasive, objective marker of disease activity in IBD, use of which may help to reduce the need for endoscopic examination in some patients.

Cyclosporin Versus Infliximab in Severe Acute Ulcerative Colitis Refractory to Intravenous Steroids: A Randomized Trial[4]

D Laharie, A Bourreille, J Branche, M Allez, Y Bouhnik, J Filippi, F Zerbib, M Nachury, G Savoye, J Moreau, J-C Delchier, E Ricart, J Cosnes, A López-San Román, O Dewit, F Carbonnel, B Coffin, GA Van Assche, M Esteve, MA Färkkilä, JP Gisbert, G Bommelaer, P Marteau, S Nahon, M De Vos, D Franchimont, J-Y Mary, J-F Colombel, M Lémann

Acute severe UC is a serious and potentially lethal condition with a mortality rate of nearly 1%.[5] This condition requires proactive treatment, including early hospitalization, intensive monitoring, and/or timely colectomy. Intravenous (IV) corticosteroids are typically the first-line therapy for this condition, but medical rescue therapy may be necessary if patients do not respond to corticosteroids within 3–5 days. Both IV cyclosporine and IV infliximab are known to be effective as rescue therapy.[6]

To determine which agent is more effective as rescue therapy in patients with steroid-resistant acute severe UC, researchers evaluated 111 patients with acute severe UC who were treated at 29 centers between June 2007 and August 2010. This study was the first randomized controlled trial comparing cyclosporine and infliximab in this population.

After fulfilling the criteria for IV steroid failure, patients were randomized to receive either IV cyclosporine (2 mg/kg/d for 1 week, followed by oral cyclosporine through Day 98; n=55) or IV infliximab (5 mg/kg at Weeks 0, 2, and 6; n=56). IV steroid failure was defined as a Lichtiger Index score greater than 10 after at least 5 days of treatment with IV methylprednisolone at a dose of at least 0.8 mg/kg/d. In patients who showed a clinical response at Day 7 of rescue therapy, defined as a Lichtiger Index score of less than 10 and a decrease of at least 3 points from baseline, azathioprine was started at a dose of 2.5 mg/kg/d, and steroids were tapered according to a fixed regimen.

The primary endpoint of the study was the rate of treatment failure, which was defined as any of the following 6 outcomes: absence of clinical response at Day 7; absence of remission without steroids at Day 98 (defined as Mayo score ≤2 without any subscore >1); relapse between Day 7 and Day 98 (defined as an increase of ≥3 points on the Lichtiger Index scale compared to the prior visit leading to treatment modification); any severe adverse event leading to treatment interruption; colectomy; or fatality.

Of the 54 women and 57 men included in the modified intent-to-treat analysis, patients' median age was 37 years, and the median Lichtiger score was 12. Rates of treatment failure were found to be similar in both treatment groups: 60% with cyclosporine versus 54% with infliximab. Response rates at Day 7 were also similar for both groups: 84% with cyclosporine versus 86% with infliximab. By Day 98, colectomies had been performed in 10 patients treated with cyclosporine and 13 patients treated with infliximab. During the course of the study, 10 severe adverse events occurred in 9 patients treated with cyclosporine, and 16 serious adverse events occurred in 16 patients receiving infliximab. No deaths occurred in this study. The researchers concluded that cyclosporine is no more effective than infliximab for achieving short-term remission and avoiding urgent colectomy in acute severe UC patients who are refractory to IV corticosteroids.

Infliximab for Severe IV Steroid-Refractory Ulcerative Colitis: Can Infliximab Trough Levels Guide Our Management?[7]

M Ferrante, V Ballet, V Geskens, S Vermeire, GA Van Assche, A Gils, PJ Rutgeerts

In another study examining optimal therapy for severe, IV steroid–refractory UC, researchers evaluated the long-term outcomes of maintenance therapy with infliximab and attempted to define predictors of colectomy-free survival. In particular, this study examined whether infliximab trough levels could guide clinical practice.

Overall, 10 women and 20 men (median age of 39 years) received infliximab rescue therapy (5 mg/kg) after treatment with IV steroids (median of 8 days). At the time of the first infliximab dose, median disease duration was 16 months; median C-reactive protein (CRP) level was 35.7 mg/L; median hemoglobin level was 10.7 g/dL; and median albumin level was 32.0 g/L. Extensive colitis was found in 90% of patients; 76% of patients had a Mayo endoscopic subscore of 3; and 57% had received azathioprine. Clinical response to infliximab was based on the physician's assessment, and infliximab trough levels were analyzed in 25 patients using an enzyme-linked immunosorbent assay developed by the researchers.

Initial findings showed that 23 of 30 patients (77%) achieved clinical response, 2 patients needed rescue therapy, and 5 patients required colectomy within 2 months. After a median follow-up period of 35 months, 3 initial responders were successfully bridged to azathioprine monotherapy, 13 maintained steroid-free clinical response with infliximab (3 of whom needed dose escalation to sustain response), and the remaining 7 initial responders required medical rescue therapy. Of the latter 7 patients, 3 received steroids and 4 received adalimumab; 2 of these patients required colectomy approximately 1 year after the first dose of infliximab.

All patients had detectable infliximab trough levels at Week 2. Quartile analysis did not reveal a higher colectomy rate in patients with lower trough levels (Q1, 33%; Q2, 20%; Q3, 0%; Q4, 17%; P=.323). Likewise, trough levels at Weeks 14 and 30 did not predict colectomy-free survival. Instead, colectomy-free survival was predicted by short-term mucosal healing (P=.032), normalization of CRP levels (P=.029), and short-term clinical response (Breslow P<.001). This study also found trends toward higher colectomy rates in patients with baseline hemoglobin levels less than 12 g/dL and/or a Mayo endoscopic subscore of 3 (P=.093 and P=.117, respectively). Three patients developed acute infusion reactions, and 1 patient had severe pneumonia during the follow-up period, but there were no deaths.

Overall, 53% of infliximab-maintained patients with IV steroid–refractory UC achieved a steroid-free clinical response that was sustained over a median follow-up period of 35 months; however, 23% of patients required a colectomy during this period. While this study's findings are preliminary, infliximab trough levels do not seem to predict colectomy-free survival.

Safety of Infliximab and Other Crohn's Disease Therapies: TREAT Registry Data with a Mean of 5 Years of Follow-Up[8]

GR Lichtenstein, RD Cohen, BG Feagan, BA Salzberg, M Turner, D Mink, WK Langholff, R Diamond, WJ Sandborn

To help determine the long-term safety of infliximab and other agents used in the treatment of CD, researchers examined relevant data from a total of 6,273 patients enrolled in the TREAT registry. This registry is a prospective, observational, multicenter, long-term registry designed to evaluate clinical, economic, and humanistic measures associated with the treatment of CD. The objective of this registry is to track treatments and patient outcomes over a period of at least 5 years; data are collected by physicians on a semiannual basis to document disease severity, medication use, and adverse events.[9]

Of the 6,273 patients in this study, 3,420 individuals received infliximab, yielding 17,712 patient-years of exposure; 89.9% of patients received at least 2 infliximab infusions. Another 2,853 patients received other medical therapies, resulting in a total of 13,251 patient-years of exposure. The mean follow-up period was 5.2 years. At registration, a higher proportion of infliximab-treated patients had moderate-to-severe disease compared to patients who received other therapies (30.6% vs 10.7%; P<.001); infliximab-treated patients were also more likely to have severe-fulminant disease (2.5% vs 0.6%; P<.001). Additionally, more infliximab-treated patients had been hospitalized in the year prior to study enrollment (27.2% vs 18.9%; P<.001), and more infliximab-treated patients were taking prednisone (47.8% vs 31.4%; P<.001) or immunomodulators (52.0% vs 32.1%; P<.001) at enrollment.

The current analysis showed that infusion reactions occurred in 2.8% of infusions, and 0.047% of infusions were associated with serious infusion reactions. Mortality was similar for both infliximab-treated patients and patients who received other therapies (0.56 vs 0.62 deaths per 100 patient-years; risk ratio [RR]=0.91; 95% CI, 0.68–1.21). An adjusted Cox proportional

hazards analysis showed that increased mortality risk was associated with the use of prednisone (hazard ratio [HR]=2.113; 95% CI, 1.418–3.148; *P*<.001) and narcotics (HR=1.782; 95% CI, 1.197–2.655; *P*<.001). In contrast, the association between increased mortality risk and disease severity (moderate/severe) was not statistically significant (HR=1.217; 95% CI, 0.626–2.366; *P*=.562).

The incidence of malignancies was similar in both groups: 0.43 and 0.52 per 100 patient-years among infliximab-treated patients and patients who did not receive infliximab, respectively (RR=0.83; 95% CI, 0.61–1.14). The incidence of lymphoma was also similar between the 2 groups: 0.05 and 0.06 per 100 patient-years, respectively (RR=0.80; 95% CI, 0.31–2.07). Serious infections within 3 months of an infliximab infusion occurred at a rate of 2.06 per 100 patient-years; serious infections at other times occurred at a rate of 1.42 per 100 patient-years (RR=1.45; 95% CI, 1.10–1.91; *P*=.008).

An adjusted Cox analysis using medication exposure at any time prior to the event showed that infliximab treatment approached statistical significance as a predictor of serious infections (HR=1.277; 95% CI, 0.977–1.668; *P*=.073). Other factors associated with serious infections included use of prednisone (HR=1.460; 95% CI, 1.141–1.870; *P*=.003) and use of narcotics (HR=1.732; 95% CI, 1.339–2.241; *P*<.001). Using a multivariate Cox proportional hazards regression model and examining medication exposure in the prior 6-month data collection period, the study identified several significant predictors of serious infections: severity of disease (HR=2.239; 95% CI, 1.569–3.194; *P*<.001), use of narcotic analgesics (HR=1.98; 95% CI, 1.436–2.729; *P*<.001), use of prednisone (HR=1.571; 95% CI, 1.173–2.103; *P*=.002), and use of infliximab (HR=1.431; 95% CI, 1.110–1.844; *P*=.006). In terms of other adverse events, nonfatal tuberculosis infections occurred in 2 infliximab-treated patients and 1 patient who had received other CD therapies.

In conclusion, infliximab-treated patients had similar rates of mortality and malignancy—including lymphoma—compared to patients who were not treated with infliximab, despite the fact that infliximab-treated patients had more severe CD. Although patients treated with infliximab did show an increased risk of serious infections, Cox proportional hazard analyses suggest that this risk is most strongly associated with disease severity and the use of prednisone and/or narcotics.

Long Term Remission with Certolizumab Pegol in Crohn's Disease: Efficacy Over 5 Years in Patients with No Prior Anti-TNF Agent Exposure (PRECiSE 3 Study)[10]

WJ Sandborn, DA Schwartz, S Schreiber, IC Lawrance, DL Sen, GR Lichtenstein

The aim of this study was to assess remission rates in patients who received long-term therapy with certolizumab pegol and to determine whether remission rates are affected by previous exposure to anti–tumor necrosis factor (anti-TNF) agents. Patients who completed the PRECiSE 2 study (during which they received 26 weeks of certolizumab pegol) were eligible to enter PRECiSE 3, during which they received 400 mg certolizumab pegol every 4 weeks for an additional 4.5 years. Efficacy and safety data for patients who received certolizumab pegol in PRECiSE 2 and continued with open-label treatment in PRECiSE 3 were presented in this abstract. The Harvey-Bradshaw Index (HBI) was used to measure disease activity, and remission was defined as an HBI score less than or equal to 4.[11] Using PRECiSE 2 as a baseline, remission rates were analyzed in both the PRECiSE 3 intent-to-treat population and in a subset of PRECiSE 3 patients who never received infliximab.

Of the 141 patients in the PRECiSE 3 study, 114 patients were infliximab-naïve. At the start of the PRECiSE 3 study, 75% (105/141) of the total study population and 78% (89/114) of the infliximab-naïve patients were in remission. After 1, 2, 3, 4, and 5 years, remission rates for the total PRECiSE 3 population were 75%, 84%, 82%, 79%, and 91%, respectively; in the infliximab-naïve patients, remission rates were 76%, 83%, 82%, 81%, and 89%, respectively (Table 1). When a nonresponder imputation analysis was used, remission rates for the total PRECiSE 3 population after 1, 2, 3, 4, and 5 years were 65%, 49%, 35%, 23%, and 21%, respectively; among infliximab-naïve patients, these rates were 65%, 47%, 37%, 25%, and 21%, respectively. No new safety signals were observed in this study, nor were there any unexpected serious adverse events.

The researchers concluded that continuous therapy with certolizumab pegol (400 mg) provided long-term remission among patients who initially responded to certolizumab pegol induction therapy. This finding held true both in the total PRECiSE 3 patient population and in a subset of PRECiSE 3 patients who were receiving certolizumab pegol but had not been previously exposed to infliximab.

Table 1. Remission Rates for Patients in the PRECiSE 3 Study

	Total population % remission (n/N) [95% CI]		Infliximab-naïve population % remission (n/N) [95% CI]	
	Observed	NRI	Observed	NRI
Year 1 (Week 26 of PRECiSE 3)	75 (92/123) [67–83]	65 (92/141) [57–73]	76 (74/98) [67–84]	65 (74/114) [56–74]
Year 2 (Week 78 of PRECiSE 3)	84 (69/82) [76–92]	49 (69/141) [41–57]	83 (54/65) [74–92]	47 (54/114) [38–57]
Year 3 (Week 130 of PRECiSE 3)	82 (49/60) [72–92]	35 (49/141) [27–43]	82 (42/51) [72–93]	37 (42/114) [28–46]
Year 4 (Week 182 of PRECiSE 3)	79 (34/43) [67–91]	23 (33/141) [16–30]	81 (29/36) [68–94]	25 (28/114) [17–33]
Year 4.5 (Week 206 of PRECiSE 3)	83 (30/36) [71–96]	21 (30/141) [15–28]	81 (25/31) [67–95]	22 (25/114) [14–30]
Year 5 (Week 234 of PRECiSE 3)	91 (29/32) [81–100]	21 (29/141) [14–27]	89 (24/27) [77–100]	21 (24/114) [14–29]

CI=confidence interval; NRI=nonresponder imputation analysis.

Is Weight-Based Dosing of Adalimumab or Certolizumab Pegol Associated with Higher Efficacy in Patients with Crohn's Disease (CD)?[12]

W Blonski, MT Osterman, CM Brensinger, AM Buchner, GR Lichtenstein

Anti-TNF therapy is recommended in adult CD patients who have an inadequate response to conventional therapy, either because they are refractory to conventional therapy or because they cannot tolerate such treatment.[13,14] Currently, clinicians have several anti-TNF agents from which to choose; the US Food and Drug Administration (FDA) has approved infliximab, adalimumab, and certolizumab pegol for treatment of patients with CD. Infliximab is dosed based on the patient's weight, but certolizumab pegol and adalimumab do not employ weight-based dosing. The aim of this study was to assess whether the patient's weight influences the efficacy of treatment with adalimumab and/or certolizumab pegol.

All outpatient records in an electronic database were retrospectively reviewed to identify CD patients who had been treated with adalimumab and/or certolizumab pegol between October 1998 and October 2010. Adalimumab was administered subcutaneously at a dose of 160 mg at Week 0, 80 mg at Week 2, and 40 mg every other week thereafter (or weekly, if needed). Certolizumab pegol (400 mg) was administered subcutaneously at Weeks 0, 2, and 4, followed by maintenance doses every 4 weeks thereafter. The disease activity of patients treated with adalimumab and/or certolizumab pegol therapy was evaluated via HBI.[14] Clinical response was defined as a reduction in HBI score of at least 3 points from baseline, and clinical remission was defined as an HBI score less than or equal to 4. Using logistic regression analyses, several variables were assessed as potential predictors of response and/or remission, including age, sex, duration of CD, previous exposure to infliximab, duration of treatment with adalimumab and/or certolizumab pegol, body weight, and body mass index (BMI).

A total of 2,177 consecutively treated CD patients were identified. Eighty-four patients (29 male and 55 female) had been treated with adalimumab and/or certolizumab pegol; patients' mean age was 36.4 years and their mean CD duration was 12.2 years. Of these 84 patients, 58 (69%) had been treated with adalimumab alone, 3 (4%) had received certolizumab pegol alone, and 23 (27%) had received adalimumab followed by certolizumab pegol. Sixty of these patients (71%) had been previously treated with infliximab. Of the 58 patients treated with adalimumab alone, 26 (45%) responded to the drug, 16 maintained remission, and 16 did not respond. Of the 3 patients treated with certolizumab pegol alone, 2 responded, and 1 did not respond. Of the 23 patients who received adalimumab followed by certolizumab pegol, 7 responded, 9 did not respond, 5 maintained remission, and 2 had insufficient records to evaluate the efficacy of certolizumab pegol.

None of the factors analyzed via multivariate analysis was found to be independently predictive of clinical response or remission. These results suggest that neither weight- nor BMI-related dosing is associated with the likelihood of clinical remission or response in patients

treated with certolizumab pegol and/or adalimumab. Therefore, weight-based dosing of adalimumab and certolizumab pegol does not appear to be necessary.

Adalimumab and Certolizumab Pegol for the Treatment of Crohn's Disease: Does BMI Make a Difference?[15]

JM Moore, DB Beaulieu, SN Horst, S Armstrong, PA Duncan, JH Wagnon, C Duley, J Ward, A Rosenbury, DA Schwartz

In a similar study, Moore and colleagues sought to determine whether BMI affected patient response in a cohort of CD patients treated with adalimumab or certolizumab pegol. This retrospective study analyzed data from patients who received adalimumab or certolizumab pegol at a tertiary care center between October 2009 and June 2010. Collected data included gender, BMI, disease type, prior use of biologic agents and/or immunomodulators, use of tobacco, need for micro-reinduction (mRI), and endoscopy findings. Patients were categorized as normal weight (BMI <25 kg/m^2), overweight (BMI >25 kg/m^2), or obese (BMI >30 kg/m^2). Health-related quality of life was assessed before and after treatment using the 10-question Short Inflammatory Bowel Disease Questionnaire (S-IBDQ). Disease activity scores as measured by HBI were also reported prior to and following initiation of biologic treatment. Response was defined as a change of at least 3 points in HBI score; remission was defined as an HBI score less than 3.[14]

This study evaluated 41 CD patients who were treated with injectable biologic agents (19 with adalimumab and 22 with certolizumab pegol). Of these patients, 58% were women, and patients' median age was 31 years (range, 20–73 years). The median time to follow-up after institution of biologic treatment was 54 days (range, 22–245 days). Twenty-one patients were normal weight, 20 were overweight, and 6 were obese.

No differences were found between normal-weight and overweight patients with regard to prior history of infliximab treatment (47% vs 40%) or prednisone use (20% vs 38%). Similarly, no significant differences in mean HBI scores were observed between normal-weight and overweight patients at initial evaluation (5.5±3.8 vs 6.0±8.1) or follow-up (3.3±3.4 vs 3.0±5.6). HBI score decreased significantly between initial evaluation and follow-up in both groups (P<.05).

Response or remission was achieved in 18 of 20 overweight patients (90%) and in 15 of 21 normal-weight patients (71%). All 6 obese patients (100%) achieved response or remission. More normal-weight patients than overweight patients required mRI (57% vs 20%; P<.05). S-IBDQ scores increased significantly with treatment in normal-weight, overweight, and obese patients.

In conclusion, this study found that the performance of certolizumab pegol and adalimumab was not affected by patients' BMI. However, it should be noted that this study analyzed a relatively small cohort of patients.

Cost-Effectiveness of Third-Line Anti-TNF Therapy Compared to Natalizumab in Patients with Moderate-to-Severe Crohn's Disease with Two Prior Anti-TNF Failures[16]

AN Ananthakrishnan, C Hur, JR Korzenik

Three drugs—infliximab, adalimumab, and certolizumab pegol—are currently approved for treatment of moderate-to-severe CD; the goal of treatment with any of these agents is to induce and maintain remission. Unfortunately, a substantial number of patients either fail to respond to these agents or lose response over time.[17,18] Moreover, prior failure is associated with lower rates of response to subsequent anti-TNF therapy.[19] Thus, clinicians face a challenge when deciding how to manage a patient who has failed 2 anti-TNF agents, as they must often choose between using a third anti-TNF agent or initiating treatment with natalizumab, an integrin inhibitor that acts via a distinct biologic mechanism.

To compare the performance of certolizumab pegol as third-line anti-TNF therapy versus natalizumab for treatment of patients with moderate-to-severe CD, a decision analysis model was constructed based on published estimates of the efficacies of third-line anti-TNF therapy and natalizumab.[20,21] A 1-year time frame was used for the analysis, and costs were expressed in 2010 US dollars. An incremental cost-effectiveness ratio (ICER) was calculated, and sensitivity analyses were performed by varying costs and efficacy estimates. A base-case scenario assumed that patients receiving certolizumab pegol would have a response rate at 2 months of 61%, and 54% of these patients were assumed to maintain response or remission throughout the year.[20] Based on findings from the ENACT trial, the estimated 2-month response rate for natalizumab was 58%, 39% of patients were assumed to have maintained remission at 12 months, and 15% of patients were assumed to have achieved clinical response.[21]

In the base-case estimate, natalizumab was found to be more effective than third-line certolizumab pegol (0.72 vs 0.71 quality-adjusted life years [QALYs]), but its use was associated with an incremental cost of $1,502, yielding an

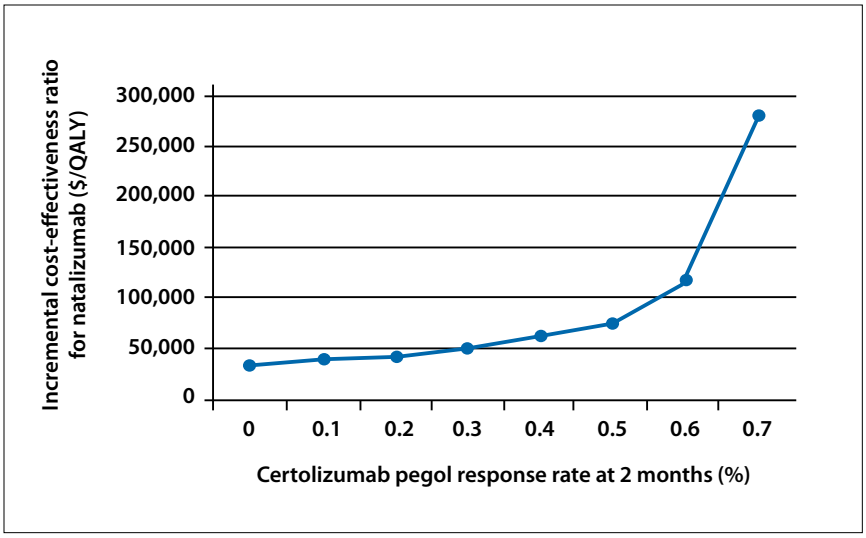

Figure 1. The incremental cost-effectiveness ratio for natalizumab was acceptable (assuming a willingness-to-pay threshold of $80,000/quality-adjusted life year [QALY]) when the 2-month response rate for certolizumab pegol was 50% or lower.

ICER of $120,976 per QALY. If the 2-month response rate with certolizumab pegol was estimated to be 50% or lower, however, then treatment with natalizumab had an acceptable ICER, assuming a willingness-to-pay threshold of $80,000 per QALY (Figure 1). On the other hand, a 25% reduction in the cost of certolizumab pegol yielded high ICERs for natalizumab at all certolizumab pegol response rates above 10%.

In a hypothetical cohort of 100,000 patients, both treatment strategies resulted in similar numbers of patients achieving clinical remission or response after 1 year: 61,051 with certolizumab pegol versus 60,111 with natalizumab. Given the findings from this study, using a third anti-TNF agent such as certolizumab pegol to treat patients with moderate-to-severe CD who have failed 2 other anti-TNF therapies is a cost-effective strategy, provided this agent can achieve response rates of at least 50% at 2 months.

Neurological Complications of TNF-α Antagonists: A 10 Year (2000–2009) Review of the Food and Drug Administration Adverse Event Reporting System Database. Results of the REFURBISH Study[22]

D Parakkal, H Sifuentes, M Sherid, ML Marshall, ED Ehrenpreis

TNF-α antagonists are widely used in the treatment of IBD, rheumatoid arthritis (RA), psoriasis, and ankylosing spondylitis. While generally safe, anti-TNF agents have been associated with occasional reports of neurologic adverse events, including demyelination, peripheral neuropathy, optic neuritis, and Guillain-Barré syndrome (GBS). To verify these infrequent reports, a review was conducted of neurologic adverse events collected via the FDA's Adverse Event Reporting System (AERS), which is available for public access.

In the current study, reports from the FDA AERS were searched to identify neurologic adverse reactions associated with anti-TNF biologic medications; data from January 1, 2000 through December 31, 2009 were included. Reports were searched for any neurologic adverse events associated with etanercept, infliximab, adalimumab, or certolizumab pegol; search terms included progressive multifocal leukoencephalopathy, demyelination, neuritis, neuropathy, leukoencephalopathy, GBS, myelopathy, myelitis, JC virus infection, radiculopathy, palsy, plegia, and aseptic meningitis.

A total of 529 adverse event reports were identified; 483 of these cases had not been previously reported in the literature. These reports included 224 cases involving etanercept (42.3%), 155 cases involving adalimumab (29.3%), 147 cases involving infliximab (28%), and 2 cases involving certolizumab pegol (0.4%). RA was associated with 212 case reports (40.1%), psoriasis with 99 case reports (18.7%), CD with 85 case reports (16.1%), ankylosing spondylitis with 52 case reports (9.8%), juvenile RA with 19 case reports (3.6%), UC with 9 case reports (1.7%), and all other conditions with 53 case reports (10%).

Overall, the study identified 141 cases of peripheral neuropathy, 136 cases of demyelination, 71 cases of optic neuritis, 33 cases of GBS, 17 cases of leukoencephalopathy, 13 cases of transverse myelitis, 10 cases of chronic inflammatory demyelinating polyneuropathy, and 1 case of posterior reversible encephalopathy syndrome. In addition, this study identified 3 cases of progressive multifocal leukoencephalopathy; 2 of these

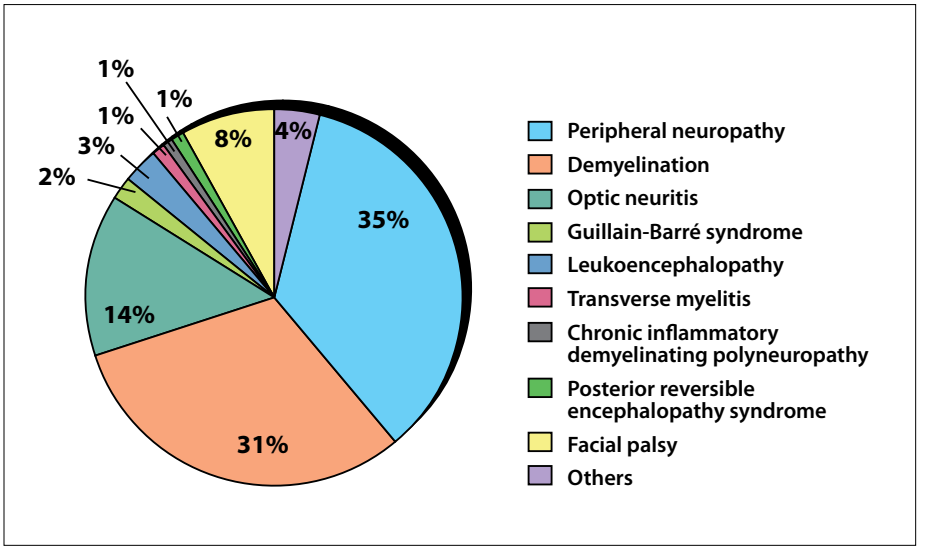

Figure 2. Neurologic complications reported in 94 patients with inflammatory bowel disease.

cases occurred in RA patients (1 involving etanercept and 1 involving infliximab), and the third case occurred in an infliximab-treated patient with cartilage hair hypoplasia syndrome. In patients who had received biologic agents for the treatment of IBD, the most common adverse events were peripheral neuropathy (33 cases), demyelination (29 cases), and optic neuritis (13 cases; Figure 2).

Overall, this systematic review of data from the FDA AERS identified many more neurologic adverse events associated with TNF-α antagonists than have been reported in the worldwide medical literature. These types of neurologic complications are significant adverse events, and they require careful surveillance in patients receiving TNF-α antagonists.

Phase 2 Randomized Study of CP-690,550, an Oral Janus Kinase Inhibitor, in Active Crohn's Disease[23]

WJ Sandborn, S Ghosh, J Panes, I Vranic, J Spanton, W Niezychowski

CP-690,550 (CP) is a novel, oral Janus kinase (JAK) inhibitor that is currently being investigated as a new therapy for IBD. In vitro studies have shown that CP can inhibit JAK1, JAK2, and JAK3, with functional specificity for JAK1 and JAK3 over JAK2. The inhibition of JAK1 and JAK3 is expected to block signaling through the common γ-chain–containing cytokines—including interleukin-2 (IL-2), IL-4, IL-7, IL-9, IL-15, and IL-21—which may provide a novel therapeutic approach to the treatment of IBD, including CD. The goal of this phase II trial was to evaluate the safety and efficacy of CP in patients with moderate-to-severe CD.

This study was a multicenter, double-blind, phase II trial involving 139 patients with moderate-to-severe CD (defined as a Crohn's Disease Activity Index [CDAI] score of 220–450 points). Patients were randomized to receive either placebo or CP (at doses of 1 mg, 5 mg, or 15 mg) twice daily for 4 weeks. Concomitant treatment with 5-aminosalicylic acid, oral corticosteroids, and/or antibiotics was permitted, but immunosuppressants and anti-TNF agents were removed from patients' treatment regimens prior to the start of the trial. The primary endpoint of this study was the percentage of patients who achieved a reduction in CDAI score of at least 70 points by Week 4 (Response 70). Secondary endpoints included remission (defined as CDAI score <150 points) and reduction in CDAI score of at least 100 points (Response 100). Of the 139 patients in this study, 28% had received immunosuppressant therapy and 7% had received anti-TNF therapy in the 3 months prior to study entry.

For Response 70, the differences in response rates compared to placebo were 5% for the 5 mg CP dose (80% CI, -6% to 16%) and 7% for the 15 mg CP dose (80% CI, -7% to 21%); for Response 100, differences in response rates versus placebo were 11% for the 5 mg dose (80% CI, -1% to 23%) and 13% for the 15 mg dose (80% CI, -1% to 26%).

In terms of safety, the overall incidences of adverse events and serious adverse events were similar among CP-treated and placebo-treated patients. There was a dose-dependent increase from baseline in low-density lipoprotein (LDL) cholesterol at Week 8 in the 15 mg CP group (11 mg/dL), but no other laboratory findings showed clinically significant changes.

Overall, the study authors concluded that CP had no significant effect on clinical endpoints (as measured

Table 2. Clinical Response and Remission at Weeks 6 and 8 with Ustekinumab or Placebo

	Placebo	Ustekinumab 1 mg/kg	Ustekinumab 3 mg/kg	Ustekinumab 6 mg/kg	Ustekinumab combined
Clinical response at Week 6	23.5%	36.6%*	34.1%	39.7%*	36.8%*
Clinical response at Week 8	17.4%	32.1%*	31.8%*	43.5%*	35.8%*
Clinical remission at Week 6	10.6%	16.0%	15.9%	12.2%	14.7%
Clinical remission at Week 8	10.6%	17.6%	17.4%	18.3%	17.8%

*$P<.05$ by Cochran-Mantel-Haenszel chi-square test.

by CDAI) after 4 weeks of treatment. However, the study did observe a dose-dependent treatment effect on CRP levels, and the 15 mg CP dose showed a treatment effect on FC levels.

Phase 2 Study of CP-690,550, an Oral Janus Kinase Inhibitor, in Active Ulcerative Colitis[24]

WJ Sandborn, S Ghosh, J Panes, I Vranic, C Su, J Spanton, W Niezychowski

In a similar study, CP was evaluated in patients with moderate-to-severe active UC. To be enrolled in this study, patients had to have UC (without proctitis), a Mayo score of at least 6, and an endoscopic subscore of at least 2. A total of 194 patients (30% of whom had had prior exposure to anti-TNF agents) were randomized to receive CP (at doses of 0.5 mg, 3 mg, 10 mg, or 15 mg) or placebo twice daily for 8 weeks. Patients were allowed to continue concomitant therapies except for immunosuppressants and anti-TNF agents.

The primary endpoint of the study was clinical response rate at Week 8; clinical response was defined as a decrease in Mayo score of at least 3 points and at least 30%, plus a decrease in rectal bleeding subscore of at least 1 point or an absolute subscore less than or equal to 1. Secondary endpoints included clinical remission at Week 8 (defined as a Mayo score ≤2 with no subscore >1), endoscopic remission at Week 8 (defined as an endoscopic subscore of 0), and endoscopic response at Week 8 (defined as a decrease in endoscopic subscore of ≥1 point). Statistical inferences were calculated based on a dose-response model fitted to each endpoint. FC and CRP levels were also measured and reported as percent change from baseline.

Analysis of the intent-to-treat population at Week 8 showed that a clinical response was achieved in 32.3% of the 0.5 mg CP group, 48.5% of the 3 mg CP group, 60.6% of the 10 mg CP group, and 77.6% of the 15 mg CP group, versus 41.7% of patients in the control group. Rates of clinical remission in the intent-to-treat population were 12.9%, 33.3%, 48.5%, and 40.8% in the 0.5 mg, 3 mg, 10 mg, and 15 mg CP groups, respectively, versus 10.4% in the control group.

Incidences of adverse events were similar between CP-treated patients and control patients. At Week 8, a dose-dependent increase from baseline was noted for LDL cholesterol (12 mg/dL in the 15 mg CP group), but no other clinically significant changes in laboratory values were observed. The authors concluded that treatment with CP was associated with dose-dependent improvement in clinical response and remission rates in patients with moderate-to-severe UC; moreover, CP was generally well tolerated.

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 2b Study of Ustekinumab, a Human Monoclonal Antibody to IL-12/23p40, in Patients with Moderately to Severely Active Crohn's Disease: Results Through Week 22 From the Certifi Trial[25]

WJ Sandborn, C Gasink, L-L Gao, M Blank, J Johanns, C Guzzo, BE Sands, SB Hanauer, SR Targan, PJ Rutgeerts, S Ghosh, W de Villiers, R Panaccione, GR Greenberg, S Schreiber, S Lichtiger, BG Feagan

In another study of a new agent, researchers evaluated the safety and efficacy of ustekinumab, a human monoclonal antibody to IL-12 and IL-23. IL-12 and IL-23 have both been implicated in the pathophysiology of CD, so targeting these cytokines could potentially provide another way to treat this condition.[26,27] In this phase IIb study, researchers evaluated the safety and efficacy of ustekinumab for inducing and maintaining clinical response and remission in patients with moderate-to-severe CD. All patients in this study had a CDAI score of 220–450 points and had previously failed or were intolerant to at least 1 anti-TNF agent.

A total of 526 patients were randomized to receive either IV placebo or IV ustekinumab (1 mg/kg, 3 mg/kg, or 6 mg/kg) at Week 0. Patients who received IV ustekinumab induction therapy and were either responders (decrease in CDAI score ≥100 points) or nonresponders at Week 6 were then separately re-randomized at Week 8 to maintenance therapy with 90 mg ustekinumab or placebo. This maintenance therapy was administered subcutaneously at Weeks 8 and 16, and patients were followed through Week 22. For patients who showed a response to IV placebo, maintenance therapy consisted of subcutaneous placebo at Weeks 8 and 16; placebo nonresponders received subcutaneous ustekinumab at Week 8 (270 mg) and Week 16 (90 mg). The primary endpoint of the study was clinical response at Week 6 (defined as a reduction in CDAI score of ≥100 points from baseline).

Of the 526 patients randomized to ustekinumab or placebo, median disease duration was 10.3 years, and patients' mean baseline CDAI score was 324 points. Approximately half (48.8%) of patients had failed 2 or more anti-TNF agents, and 30.4%, 72.2%, and 33.5% of patients fulfilled the criteria for primary anti-TNF nonresponse, secondary anti-TNF nonresponse, and anti-TNF intolerance, respectively.

The primary study endpoint (clinical response at Week 6) was achieved by 39.7% of patients in the 6 mg/kg ustekinumab group and 23.5% of patients in the placebo group (P=.005). This study found no significant differences in clinical remission at Week 6; however, the 6 mg/kg ustekinumab group showed improvement in rates of clinical response and clinical remission by Week 8 (Table 2). Compared to placebo, all doses of ustekinumab showed statistically significant changes at Week 6 in CDAI scores, CRP levels, fecal lactoferrin levels, FC levels, Inflammatory Bowel Disease Questionnaire scores, and 70-point decreases in CDAI scores.

Among patients who showed a clinical response to ustekinumab at Week 6, 41.7% (30/72) of patients who received subcutaneous ustekinumab as maintenance therapy were in clinical remission at Week 22, compared to 27.4% (20/73) of patients who received subcutaneous placebo (P=.029). Rates of clinical response at Week 22 were 69.4% and 42.5%, respectively (P<.001).

Adverse events, serious adverse events, and infections occurred at similar rates among patients in the ustekinumab-treated and placebo-treated groups; this finding held true during both the induction and maintenance phases of the study. No deaths, serious opportunistic infections, cases of tuberculosis, malignancies, or major adverse cardiovascular events were reported through Week 22. Infusion and injection site reactions were uncommon in both groups, and none of these reactions were serious.

The researchers concluded that ustekinumab can successfully induce and maintain clinical response in patients with moderate-to-severe CD who had previously failed anti-TNF therapy. Furthermore, the proportion of Week 6 responders who achieved clinical remission during the maintenance phase of the trial was significantly higher in the ustekinumab-treated group than the placebo group. Both IV and subcutaneous ustekinumab were also well tolerated.

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Commentary

Gary R. Lichtenstein, MD

One dilemma many gastroenterologists face when treating patients with CD is that we cannot accurately predict which patients are likely to have a more severe course of disease in the future. In an effort to better determine which factors are predictive of a severe disease course, Cosnes and colleagues analyzed data that were prospectively collected from 1995 to 2009. This 15-year, population cohort–like study identified several factors that are predictive of severe disease, including rectal involvement, smoking, and low educational level. Knowledge of these factors now allows clinicians to more aggressively treat patients with these and other characteristics that predict severe disease, thus helping to guide clinical management.

In the second study reviewed in this supplement, fecal calprotectin (FC) was considered as a possible predictor of disease activity and histologic severity. To date, endoscopy has been the gold standard for evaluating patients with IBD. However, endoscopy is invasive, so researchers have sought to find alternative techniques that can more easily assess disease activity. As part of this effort, Chung-Faye and coworkers evaluated the utility of FC as a marker of disease activity. They found a strong correlation between FC levels and histology scores, with high FC levels being strongly predictive of active disease. This finding suggests that FC might be used as a noninvasive marker for disease activity in patients with IBD, potentially lessening the need to perform endoscopy in some individuals. However, the sensitivity and specificity of FC in this study were only 83% and 74%, respectively. Thus, we are not yet to the point where this testing can completely replace endoscopy; rather, it serves as a supplement to endoscopy.

In a landmark study presented at the 2011 Digestive Disease Week (DDW) meeting, Laharie and colleagues compared cyclosporine versus infliximab for the treatment of severe acute UC in corticosteroid nonresponders. While both cyclosporine and infliximab are known to be effective in this setting, there has been no prior randomized trial comparing these treatments. In this study, both groups showed similar rates of treatment failure, response at Day 7, colectomy at Day 98, and adverse events. The overall conclusion of the study was that cyclosporine was no more effective than infliximab for achieving short-term remission and avoiding urgent colectomy. This is an important finding, as some clinicians have long maintained that cyclosporine is more effective than infliximab; however, we now have data from a well-designed, well-controlled trial showing that both agents have similar efficacy.

Another study related to severe, steroid-refractory UC sought to determine whether infliximab trough levels can guide management of this condition. Ferrante and

colleagues found that over half of patients maintained on infliximab achieved a steroid-free clinical response, and approximately 23% required colectomy. However, this study's preliminary findings indicated that infliximab trough levels were not advantageous for guiding management. New assays for the measurement of anti-TNF agents are being developed that might help us better predict disease course based on serum levels in the future, but these assays were not evaluated in this trial.

The next study reviewed in this supplement used data from the TREAT registry to assess the safety of infliximab and other CD therapies in over 6,200 patients. In this study, my colleagues and I aimed to explore safety findings associated with long-term infliximab treatment; specifically, we were interested in whether long-term infliximab treatment was associated with increased rates of mortality or malignancy (particularly lymphoma). By comparing infliximab-treated patients to patients who received other CD treatments, we determined that infliximab-treated patients had more severe CD upon entry into the registry, but they did not have a higher risk of adverse events. Clinicians should note that infliximab-treated patients experienced a mild increase in the risk of serious infections, and there was also an increased risk of serious infections associated with disease severity. In addition, it has been recognized for many years that the use of prednisone and/or narcotics is associated with an increase in infectious complications. It is important to recognize that this study did not suggest any increase in rates of malignancy or lymphoma in patients taking infliximab compared to patients who received conventional medical therapy.

Another long-term study looked at rates of remission in CD patients treated with certolizumab pegol; this study sought to measure overall remission rates and determine whether these rates were affected by patients' prior exposure to anti-TNF agents. This study by Sandborn and colleagues found that continuous maintenance with certolizumab pegol yielded long-term remission in patients who initially responded to this drug, and this finding held true in the subset of patients who had no exposure to anti-TNF therapy prior to starting certolizumab pegol. This study, the longest prospective follow-up study of anti-TNF therapy conducted to date, provides reassurance that certolizumab pegol will continue to prove effective in patients receiving long-term maintenance therapy.

One question related to both certolizumab pegol and adalimumab is whether weight-based dosing might be associated with improved treatment efficacy. In a study by Blonski and colleagues, patients treated with certolizumab pegol or adalimumab were retrospectively evaluated, and no association was found between weight or BMI and the likelihood of clinical remission or response. Overall, this small study suggested that weight-based dosing of adalimumab and certolizumab pegol does not seem to be necessary; however, a larger study including both obese patients and patients with BMIs less than 15 kg/m^2 (ie, patients on both ends of the weight spectrum) would be beneficial.

A similar study by Moore and colleagues compared normal-weight versus overweight patients who were treated with adalimumab or certolizumab pegol. Again, this study found that the percentage of patients who achieved response or remission was similar in both groups, indicating that the efficacy of certolizumab pegol and adalimumab does not seem to be influenced by patients' BMIs. As with the study by Blonski and colleagues, an important caveat is that this study involved only a small number of patients; a larger study is needed to explore the full potential impact of weight-based dosing in this population.

Another question regarding anti-TNF therapy is what to do when the first or second anti-TNF agent fails. In a cost-effectiveness study designed to address this question, Ananthakrishnan and colleagues compared anti-TNF therapy versus natalizumab for the treatment of moderate-to-severe CD in patients who had previously failed 2 anti-TNF agents. This analysis found that the most cost-effective strategy was to use a third anti-TNF agent such as certolizumab pegol rather than resorting to natalizumab. An important caution regarding this conclusion is that the authors assumed that certolizumab pegol would yield a response rate of 50% at 2 months; if this assumption does not accurately reflect clinical practice, then the study's findings may not be valid. Several previous series have suggested that patients can benefit from a third anti-TNF agent, and this analysis confirms the previously reported clinical findings.

While anti-TNF agents are generally effective, clinicians still have some concerns when using these drugs. To analyze neurologic complications associated with the use of TNF-α antagonists, Parakkal and coauthors performed a 10-year review of data from the FDA AERS. In this study, a search was performed to identify neurologic adverse events associated with biologic agents that occurred between January 2000 and December 2009. Given the widespread use of biologic medications, the relatively small number of neurologic complications identified in this study is comforting. However, estimates suggest that only approximately 10% of adverse events are reported to AERS, so this study's conclusions are probably limited by an underreporting bias. Another factor that needs to be considered when reviewing these data is that some researchers have reported a higher incidence of neurologic adverse events in IBD patients than in the general population—even in the absence of anti-TNF therapy—so some of the observed cases may be due to IBD itself rather than patients' treatments. Nonetheless, this study identified cases of peripheral neuropathy, demyelination, optic neuritis, GBS, leukoencephalopathy, transverse myelitis, and polyneuropathy. Because these serious conditions were shown to be associated with use of biologic agents, albeit

rarely, I recommend that anti-TNF therapy be avoided in patients who have previously had any of these conditions.

Finally, some of the studies presented at the 2011 DDW meeting assessed new agents being considered as novel treatments for IBD. One such study was a phase II study of CP, an oral JAK inhibitor known as tofacitinib (formerly tasocitinib). This compound inhibits JAK1, JAK2, and JAK3 and is thought to block cytokine signaling. The interleukins thought to be blocked by this inhibitor include IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. In this multicenter, double-blind, phase II trial by Sandborn and colleagues, 139 patients with moderate-to-severe CD were randomized to receive the test agent (via 1 of 3 dosing regimens) or placebo twice daily for 4 weeks. Concurrent use of mesalamine, steroids, and antibiotics was permitted, but immune modulators and anti-TNF agents were withdrawn prior to the start of the study. Overall, this study found little difference in response rates or remission rates between the active treatment group and the placebo group.

While these results are somewhat underwhelming, another phase II trial evaluating this agent in 194 UC patients yielded more promising results. In this study, also by Sandborn and coworkers, patients were randomized to 1 of 4 dosing regimens or placebo for a treatment duration of 8 weeks. Clinical response was the primary study endpoint, and secondary endpoints included clinical remission, endoscopic response, and endoscopic remission. Response rates in the higher-dosage groups were 61–78%, versus 42% in the placebo group; remission rates were 41–49% in the higher-dosage groups, versus 10% in the placebo group. The authors therefore suggested that treatment with CP was associated with a dose-dependent improvement in clinical response and remission among patients with moderate-to-severe UC. Overall, this agent seems better suited for use in patients with UC, and future trials of this agent seem likely.

The last abstract reviewed in this supplement presented data from a multicenter, randomized, double-blind, placebo-controlled, phase II study of ustekinumab, a monoclonal antibody to IL-12/23p40. Ustekinumab inhibits IL-12 and IL-23, both of which have been implicated in the production of proinflammatory cytokines, so researchers are hopeful that ustekinumab might reduce inflammation in CD. In this trial by Sandborn and colleagues, patients had moderate-to-severe CD and had failed or were intolerant to at least 1 anti-TNF agent. Patients were randomized to receive IV ustekinumab (at 1, 3, or 6 mg/kg) or placebo at baseline. At Week 8, patients were classified as responders (if their CDAI score decreased by at least 100 points) or nonresponders (if they did not achieve this endpoint). After induction therapy, patients were re-randomized to maintenance therapy, subcutaneous placebo, or subcutaneous ustekinumab (270 mg at Week 8 and 90 mg at Week 16). They were then followed through Week 22. At Week 8, 18.3% of the group that received 6 mg/kg ustekinumab achieved clinical remission, compared to 10.6% of placebo-treated patients. Clinical responses were also seen in the lower-dose groups at Week 8: 32.1% of patients receiving 1 mg/kg ustekinumab showed a clinical response at Week 8, as did 31.8% of patients receiving the 3 mg/kg dose ($P<.05$ for both comparisons versus placebo). At Week 22, 41.7% of responders on subcutaneous ustekinumab were in clinical remission, versus 27.4% of patients who received subcutaneous placebo ($P=.029$). At that time point, 69.4% of patients on subcutaneous ustekinumab were classified as having achieved a clinical response, compared to 42.5% of placebo-treated patients ($P<.001$). Thus, ustekinumab seems to be effective for the treatment of active CD. This drug was able to induce clinical response during the induction phase of the study, and the proportion of Week 6 responders who achieved clinical remission during the maintenance phase of the study was greater in the ustekinumab group than the control group. In addition, active treatment also yielded significant changes in inflammatory markers, including CRP, fecal lactoferrin, and FC. Ustekinumab was also well tolerated. Thus, this agent appears to hold promise as a possible new treatment for CD.

Overall, the abstracts presented at the 2011 DDW meeting are very important for clinical practice. The 2 new agents discussed above look promising—specifically, the oral JAK inhibitor tofacitinib (CP) in UC and ustekinumab in CD—and there is much hope that these agents (or others) can successfully graduate from the bench to the bedside, where they can help patients who suffer from these debilitating disorders. Biologic agents also continue to hold significant hope for the future, given the successes that have been seen with infliximab, adalimumab, and certolizumab pegol. Many clinicians are optimistic about the potential for future treatments that are similar to these agents (although perhaps acting by different mechanisms) and that have a favorable safety profile. Continued research and development is critical to continue the efforts that have been initiated to date.

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