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Emerging Issues in Gastroenterology and Hepatology

A Review of Selected Topics and Presentations
from Digestive Disease Week
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Target Audience: This activity has been designed to meet the educational needs of gastroenterologists and hepatologists involved in the management of patients with hepatic encephalopathy and inflammatory bowel disease.

Statement of Need/Program Overview:

The primary goals of hepatic encephalopathy (HE) treatment are to prevent episodic deterioration of cognitive function, provide salvage therapy to patients experiencing episodic deterioration, and produce improvements in patients with persistent or minimal HE. HE can be cured with liver transplantation, but not all patients are eligible for this procedure. The current standard treatment for HE in the United States is lactulose. It is often poorly tolerated by patients, which may affect compliance. Standard antibiotics for HE include neomycin, as well as rifaximin and metronidazole.

The place of biologic therapies in the overall therapeutic armamentarium for Crohn's disease must be understood, in terms of sustaining treatment benefit and minimizing risk associated with combination therapies that include steroids or immunomodulators. Recent evidence regarding the use of biologic monotherapies versus combinations and top-down versus step-up strategies should be further explored and incorporated into current treatment paradigms. Until these issues have been definitively addressed, physicians need to have up-to-date information on the nuances of current controversies in order to make well-considered recommendations for ongoing treatment.

As new data are announced at scientific meetings, summaries and analysis by expert opinion leaders can assist clinicians in detecting the disease and making effective decisions with regard to therapeutic options. An abstract summary including important hepatic encephalopathy and IBD-related data from the 2009 DDW meeting would provide an excellent educational resource for readers of *Gastroenterology & Hepatology*.

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

1. Describe the pathophysiology of hepatic encephalopathy (HE).
2. Discuss efficacy of current therapeutic options for HE.
3. Assess recent research into the evolving role of biologic therapies in the treatment of Crohn's disease.

Accreditation Statement: This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Postgraduate Institute for Medicine (PIM) and *Gastroenterology & Hepatology*.

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Advances in Hepatic Encephalopathy

S1841 The Role of Small Intestinal Bacterial Overgrowth in Hepatic Encephalopathy (HE)[1]

IS Weisberg, AB Jesudian, KC Barboza, BP Bosworth, TC Liu, S Sigal

Ammonia is a neurologic toxin that is believed to play a central role in the pathogenesis of hepatic encephalopathy (HE). Various sources of ammonia have been identified, including ingested nitrogenous compounds and glutaminase-mediated deamination of glutamine.[2] Intestinal bacteria which produce ammonia are also thought to have an important role in the development of HE. Patients with cirrhosis may be at an increased risk for impaired intestinal motility due to decreased autonomic function, leading to small intestinal bacterial overgrowth (SIBO). Weisberg and colleagues conducted this prospective study to identify the frequency of SIBO among patients with cirrhosis, and to evaluate the association between SIBO and severity of HE symptoms.[1]

A total of 34 patients with hepatitis C virus-associated cirrhosis were included in this analysis. Patients were evaluated by neuropsychometric testing to confirm the presence of HE. Lactulose breath testing was used to determine the prevalence of SIBO; the lactulose breath test was conducted by first administering 10 g of lactulose to the patient, followed by collecting breath samples over a 180-minute period. From this, breath hydrogen and methane levels were assessed. The lactulose breath test was considered positive for SIBO if one of the following criteria were met: fasting breath hydrogen levels measured 20 ppm or more, an increase in breath hydrogen levels occurred in <90 minutes, dual breath hydrogen level peaks occurred (defined as a 12 ppm increase over baseline with a decrease of ≥5 ppm prior to the second peak), or a fasting breath methane level of more than 1 ppm.

Of the 34 patients enrolled, 85% (n=29) were confirmed to have HE. Mild HE was diagnosed in 53%, and 29% had severe HE. Nearly three-quarters of patients (71%) had an abnormal lactulose breath test, indicating the presence of SIBO. Abnormal lactulose breath test results were present in 3 of the 6 patients (50%) without HE, 11 of the 18 patients (61%) with mild HE, and all 10 (100%) of the patients with severe HE. The increase in the abnormal lactulose breath test was significantly associated with an increase in the presence and severity of HE (P=.046).

From these data, Weisberg and colleagues concluded that SIBO occurs with a high frequency among patients with hepatitis C virus-associated cirrhosis. Further, the prevalence of SIBO increases with increasing presence and severity of HE. Thus, these results offer further support for the continued use of antibiotics to treat HE.

S1849 Gastrointestinal Adverse Effects of Lactulose Can Precipitate Recurrent Hepatic Encephalopathy Through Non-Compliance or Overuse[3]

JS Bajaj, DE Bell, AJ Sanyal, E Gavis, DM Heuman

The non-absorbable disaccharide sugar lactulose is one of the most widely used agents in the frontline treatment of HE, despite a lack of robust clinical evidence supporting this use.[4] A meta-analysis of 22 randomized

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trials comparing lactulose with placebo, no intervention, or antibiotics attributed only non-significant effects of lactulose on the risk of no improvement or mortality, leading to the conclusion that there was not enough evidence to support or dissuade the use of lactulose in the treatment of HE.[5] However, this conclusion is contradicted by a long and successful history of use, as well as other clinical studies that have suggested a significant benefit from lactulose.[6,7] Adverse gastrointestinal effects, including bloating and abdominal distension, are another drawback associated with the use of lactulose.[8] Overuse of lactulose is also associated with diarrhea and dehydration. These adverse effects may limit patient compliance to lactulose therapy, affecting the therapeutic efficacy of the drug and leading to recurrence of HE. Bajaj and colleagues investigated the association between lactulose use and recurrence of HE.[3]

The authors conducted a retrospective review of 119 patients with cirrhosis who were evaluated for HE in a single transplant center. The mean patient age was 55 ± 7 years, and the average Model for End-Stage Liver Disease (MELD) score was 17 ± 5. Cirrhosis was attributed to alcohol abuse in 44% of cases, hepatitis C virus in 31% of cases, and both in 10% of cases. The investigators rated a patient as noncompliant to lactulose if they experienced 2 or fewer bowel movements daily and if caregivers corroborated noncompliance at the time of HE recurrence. Lactulose overuse was determined in patients experiencing 4 or more loose bowel movements daily accompanied by dehydration at the time of HE recurrence. Recurrent HE was only considered to be associated with lactulose use if no other precipitants were identified.

Over the study period, 70% (n=83) of patients had a recurrence of HE. The repeat HE episode occurred an average of 9 ± 2 months following the initial episode of HE. Nearly half of these recurrences (48%) were associated with lactulose; of these, 40% were due to noncompliance and 8% to overuse. The vast majority of noncompliant cases were due to adverse gastrointestinal effects (90%), whereas the remainder were due to patient unwillingness to be treated (10%). Recurrent HE episodes not associated with lactulose were determined to be due to sepsis (n=24), gastrointestinal bleeding (n=4), or occurred spontaneously (n=12). Compared with these other precipitating factors (mean 2 ± 1), a significantly higher number of further hospitalizations due to HE was associated with lactulose noncompliance (mean 3 ± 3) or overuse (4 ± 2) (P=.03). However, no significant difference in duration until death or liver transplant was observed between patients experiencing recurrent HE associated or not associated with lactulose.

Bajaj and colleagues determined that HE recurrence was due to misuse of lactulose (either noncompliance or overuse) in approximately half of the patients evaluated. Further, hospitalizations due to HE recurrence were significantly more likely among these patients compared with patients whose HE recurrence was attributed to other precipitating factors. Based on these results, the investigators concluded that alternative therapies for HE, which are associated with fewer adverse gastrointestinal effects, may improve patient compliance and lead to fewer hospitalizations due to HE recurrence.

66 Rifaximin Reduces the Risk of Hospitalizations in Patients with Previous Episodes of Hepatic Encephalopathy: Results from a Phase 3 Placebo-Controlled Trial[9]

G Neff, CB Leevy, T Frederick, K Merchant, S Huang, AL Shaw, WP Forbes

Because toxins generated by intestinal bacteria are thought to be involved in the pathogenesis of HE, antibiotics have been used extensively in the treatment of HE. However, the current standard of care is inadequate, and cirrhotic patients often suffer from repeated episodes of breakthrough HE. These breakthrough episodes result in repeated hospitalizations, affecting patient quality of life and increasing economic burden. Rifaximin is an orally administered broad-spectrum antibiotic that has been granted orphan drug status by the Food and Drug Administration for the treatment of HE.[10] Considered to be a nonsystemic antibiotic, <0.4% of rifaximin is absorbed systemically; the majority of the drug concentrates in the gastrointestinal tract.[11] Unlike other antibiotics in the rifamycin drug class, rifaximin has no known interactions with other drugs metabolized by cytochrome P450 enzymes.[12-14] Rifaximin has previously been shown to be active in the treatment of HE. Here, Neff and colleagues performed a subanalysis of the RFHE3001 study to determine if rifaximin was effective to reduce the risk of hospitalization in patients with prior HE episodes.[9]

RFHE3001 was a double-blind, multicenter, international phase III study that aimed to determine the safety and efficacy of 6 months of rifaximin therapy for the maintenance of remission in patients with recurrent and overt HE. A total of 299 patients with HE associated with cirrhosis and/or portal hypertension and a MELD score of 25 or less were included in the study. Patients had 2 or more episodes of HE within 6 months of screening, defined as experiencing an increase in Conn score from 0 or 1 to 2 or greater and returning to a score of 0 or 1. Patients with active spontaneous bacterial peritonitis or requiring daily prophylactic antibiotic therapy were excluded from the study. Other exclusion criteria included having a gastrointestinal hemorrhage requiring

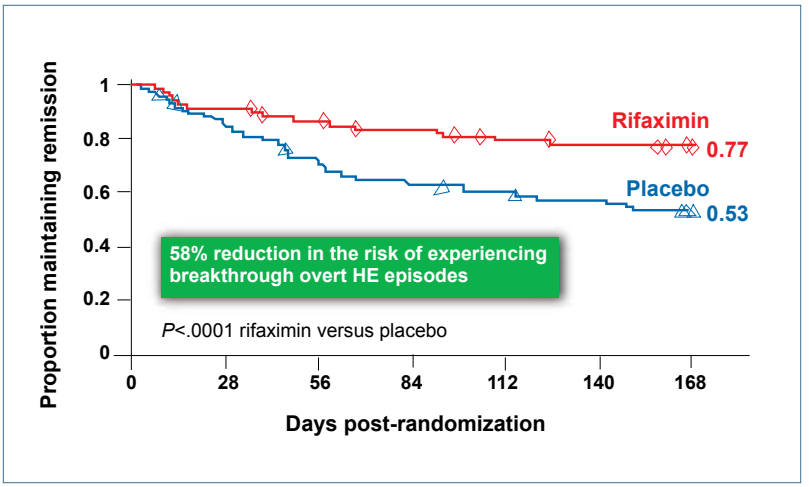

Figure 1. Time to breakthrough hepatic encephalopathy (HE) episode in the intent-to-treat population of the RFHE3001 study.

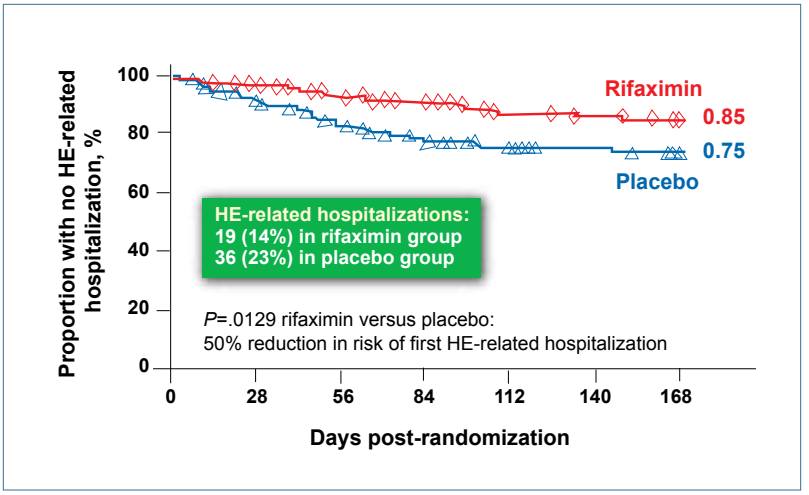

Figure 2. Average time to hepatic encephalopathy (HE)-related hospitalization in the RFHE3001 study.

hospitalization and blood transfusion within 3 months of screening, renal insufficiency, or anemia. Following an initial screening and observation period of between 3 and 7 days, patients were randomized to receive rifaximin (550 mg twice daily) or placebo. Treatment continued for 6 months, or until the patient experienced a breakthrough HE episode or was withdrawn from the study. Patients were assessed every 2 weeks during the treatment period. The baseline characteristics were evenly distributed between the two treatment arms. The primary endpoint of the RFHE3001 study was the time to first breakthrough HE episode, which was defined as either an increase in Conn score to 2 or greater or an increase of 1 point for both the Conn score and asterixis grade in patients who had a baseline Conn score of 0.

Breakthrough HE episodes were found to be significantly less common among patients randomized to receive rifaximin compared with placebo (22.1% versus 45.9%, $P<.0001$; Figure 1). This translated to a 58% reduction in the risk of a breakthrough HE episode associated with rifaximin treatment (hazard ratio 0.421, 95% CI: 0.276–0.641). Thus, the RFHE3001 trial demonstrated that rifaximin significantly decreased the risk of experiencing a breakthrough HE episode.

A key secondary endpoint of the RFHE3001 study, and the aim of this subanalysis by Neff and colleagues, was the time to first HE-related hospitalization. In the intent-to-treat population, significantly fewer HE-related hospitalizations were reported in the rifaximin group compared with the placebo group (13.6% versus 22.6%, hazard ratio: 0.50, 95% CI: 0.287-0.873, $P=.0129$; Figure 2). At 6 months, the proportion of patients receiving rifaximin who had been hospitalized for HE-related issues was also significantly decreased compared with

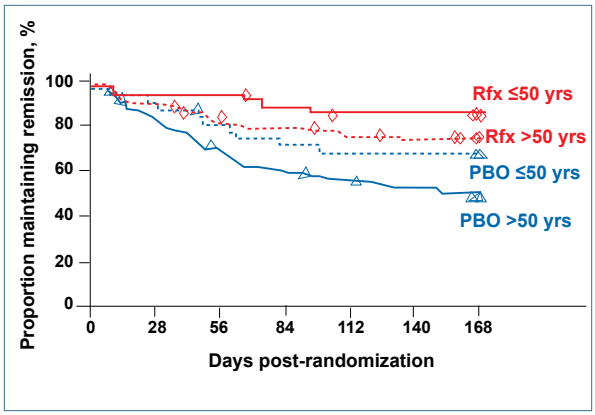

Figure 3. Time to hepatic encephalopathy (HE) breakthrough in rifaximin (Rfx) and placebo (PBO) patients, (≤50 versus >50 years of age).

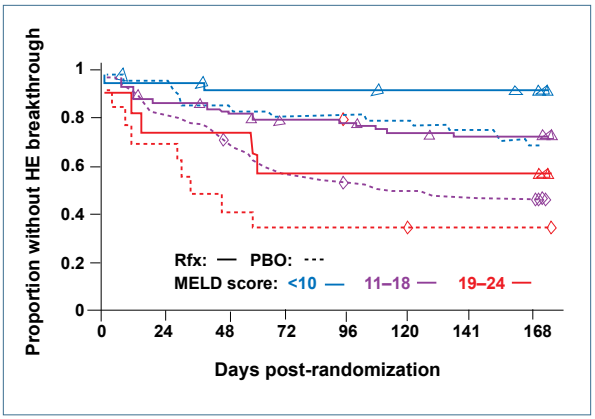

Figure 4. Time to hepatic encephalopathy (HE) breakthrough in rifaximin (Rfx) and placebo (PBO) patients (stratified by MELD score).

placebo (11% versus 21%, hazard ratio: 0.438, 95% CI: 0.238–0.807, *P*=.0064).

Based on these results, the investigators concluded that for every 9 patients who were treated with rifaximin, 1 less patient experienced an HE-related hospitalization compared with placebo. Further, they reported that rifaximin reduced the risk of all-cause hospitalization by 31% over the 6 month treatment period.

144 The Effect of Prognostic Factors On the Maintenance of Remission in Hepatic Encephalopathy Patients Treated with Rifaximin[15]

S Sigal, FF Poordad, KL Beavers, K Merchant, S Huang, AL Shaw, E Bortey, WP Forbes

RFHE3001 was a double-blind, multicenter, international phase III study which demonstrated that rifaximin (550 mg twice daily) significantly reduced the incidence of breakthrough HE episodes. While the overall goal of RFHE3001 was to compare the risk of breakthrough HE episodes among patients treated with rifaximin and placebo, Sigal and colleagues conducted a subanalysis to evaluate the effect of various prognostic factors within the RFHE3001 study.[15]

The objectives of this subanalysis were to identify prognostic factors that predicted the development of a breakthrough HE episode and to assess the effect of these factors on the maintenance of rifaximin-induced HE remission. The design and patient inclusion and exclusion criteria of the RFHE3001 study are described above. For this subanalysis, a univariate regression analysis was performed using the intent-to-treat population to identify prognostic factors. A prognostic factor was defined as potentially important with a *P*≤.10. Adjusted analyses were then performed using a proportional hazard regression model to account for the effect that strong prognostic factors may have on patient outcome.

Several clinical factors were identified that could potentially impact maintenance of response. Of these, baseline MELD score (19–24, 11–18, ≤10, *P*=.0003), the number of HE episodes within the 6 months prior to screening (>2, 2 episodes, *P*=.002), the presence or absence of transjugular intrahepatic portosystemic shunt (TIPS) (*P*=.012), patient age (>50, ≤50 years, *P*=.016), and the duration of remission at screening (>90, ≤90 days, *P*=.109) were determined to be significant independent predictors for breakthrough HE episodes. Patient sex, race, Conn score, and the presence of diabetes at screening were determined to not significantly predict breakthrough HE episodes.

When the five significant factors were used in a multivariate analysis, only age (hazard ratio: 1.89, *P*=.032) and baseline MELD score (hazard ratio: 2.02, *P*=.0003) remained significant. Among patients older than 50 years, rifaximin was associated with a 57% decrease in the risk of breakthrough HE episodes (hazard ratio: 0.427, 95% CI: 0.270–0.675, *P*=.0003; Figure 3). Although a 59% decrease in the risk of breakthrough HE episodes was associated with rifaximin use among patients 50 years old or younger, the patient size was too small to calculate the significance. Among patients with MELD scores of 10 or less, rifaximin was associated with an 81.5% decrease in the risk of breakthrough HE episodes (hazard ratio: 0.185, 95% CI: 0.042–0.815, *P*=.0123; Figure 4). The same effect was also observed among patients with

MELD scores of 11–18 (59%; hazard ratio: 0.408, 95% CI: 0.250–0.664, *P*=.0020) and 19–24 (50%; hazard ratio: 0.502, 95% CI: 0.167–1.503, *P*=NS).

The unadjusted treatment effect associated with rifaximin therapy was a 58% reduction (hazard ratio: 0.421, 95% CI: 0.276–0.641). When adjusted for age, MELD score, duration of remission, TIPS, and the number of HE episodes, this decreased to a 60% reduction (hazard ratio: 0.403, 95% CI: 0.264–0.617).

Sigal and colleagues concluded that in the RFHE3001 trial, older age and higher baseline MELD score were the most significant prognostic factors for predicting risk of breakthrough HE episodes. When adjusted for these factors, rifaximin was found to reduce the risk of breakthrough HE episodes by 60%.

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Commentary

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The colon is a major site of systemic ammonia generation, due to its role in harboring the bacterial degradation of nitrogenous substrates from the gastrointestinal tract. In fact, many decades ago, total colectomy was employed to reduce ammonia production and treat cases of severe, refractory hepatic encephalopathy (HE). The very high morbidity of this approach has since curtailed its use and further experience has shown that a prior colectomy does not entirely protect patients with end-stage liver disease from HE development. Nonetheless, the importance of enteric bacteria in the production of ammonia and the pathogenesis of HE is firmly established.

The use of nonabsorbable antibiotics in the treatment of HE has been adopted based again upon the role of enteric bacteria in the production of ammonia, and with the assumption that these antibiotics work within the colon. However, the nonabsorbable antibiotics that are used for HE do not sterilize the colon, which contains a massive density of bacteria, and there has been some speculation that the target of nonabsorbable antibiotics may be a lower-density, more select bacterial population existing in the gastrointestinal tract outside of the colon. This particular bacterial population may reside in the small bowel, in areas of bacterial overgrowth.

Weisberg and associates set out to investigate this hypothetical relationship in their study, and demonstrated—based on the lactulose breath test—a high prevalence of small intestinal bacterial overgrowth (SIBO) among patients with end-stage liver disease, with the highest prevalence of SIBO observed in patients with the most severe HE. These are interesting and thought-provoking findings that may help us better understand the mechanism of action of nonabsorbable antibiotics in HE. Although it remains unclear why patients with cirrhosis should be at greater risk for the development of SIBO, the study indicates a potentially fruitful avenue for future research. Future studies should include a suitable control group, such as patients with well-compensated cirrhosis, noncirrhotic liver disease, and normal controls. The lactulose breath test also requires further validation as an indicator of the presence of SIBO. A future large, placebo-controlled study examining HE manifestation and breath test results both before and after treatment might serve this purpose, while also further demonstrating the efficacy of nonabsorbable antibiotics in controlling SIBO and preventing future episodes of HE.

Recent meta-analysis has cast doubt on the clinical efficacy of non-absorbable dissacharides such as lactulose in the treatment of HE. The retrospective analysis by Bajaj and colleagues, however, found a significant degree of worsening of HE in patients who were noncompliant in taking this medication. What makes this study most interesting is that it demonstrates the concept that, somewhat paradoxically, overtreatment with lactulose may cause worsening HE, thus confounding the overall benefit provided by this medication. It is important to note that excessive diarrhea, fluid loss, and intravascular volume depletion in patients with end-stage liver disease can exacerbate HE. Thus, these data show the importance of caution in lactulose administration. Although some may certainly be good, there is little reason to assume that more must be better. Optimal lactulose dosing thus appears to reside within a quantitative zone typified by not too little and not too much.

Finding the right dose of lactulose for each patient with HE can prove to be challenging. Personally, I have observed a growing tendency, particularly in the management of hospitalized patients with HE, to dose-escalate lactulose if the patient is slow to recover from an episode of HE. Not only does this practice cause severe diarrhea, it carries the risk of causing dehydration. Lactulose-induced diarrhea can also result in electrolyte abnormalities such as hypernatremia. In outpatients, I have also increasingly tended to lower patients' existing lactulose dose in order to reduce the incidence of often precipitous diarrhea in addition to other gastrointestinal side effects. Clinicians should remember that there is no convincing evidence that increasing stool frequency beyond 2–3 loosely formed stools (not diarrhea) per day will lead to greater benefit in the majority of patients with HE. Further, lactulose should not be titrated based on blood ammonia levels. Dosing should be based on the patient's clinical manifestations of HE and stool frequency. If the patient experiences frequent (more than 4–5 loose stools per day), they are likely getting too much drug. If the dosage has been optimized and HE symptoms remain uncontrolled, the addition of other therapies should be considered. An initial clinical assessment of symptoms should include the patient's report of their daily function in terms of memory and concentration and their sleep patterns. Reports from family members are important to confirm patient self-assessment, and any observed alterations in personality, behavior, and consciousness. Patients should also be examined for evidence of asterixis in order to

determine the efficacy of HE treatment. Other factors to consider before elevating lactulose dose include compliance, constipation, administration of other medications that affect the central nervous system and renal function. Dietary assessment and the possibility of excessive protein intake should be considered in patients who are experiencing recurrent or refractory symptoms, but advising reduction in dietary protein should only be considered as a last resort, and is rarely indicated. Maintaining a protein intake of 1–1.5 g/kg daily is considered optimal in patients with cirrhosis, as severely limiting protein intake may result in negative nitrogen balance and aggravate loss of muscle mass.

RFHE3001, as reported by Neff and coworkers, was a double-blind, randomized, placebo-controlled, multicenter trial of rifaximin versus placebo in patients at risk for recurrent HE, most of whom were already receiving lactulose and continued to do so throughout the trial. This is the largest such study undertaken to date in the management of HE, and the first to evaluate antibiotic therapy for the prevention of HE in patients at risk for this complication due to advanced liver disease. The primary endpoint was the time to first episode of breakthrough HE and the results showed a highly significant reduction in the incidence of HE breakthrough in patients taking rifaximin (58% overall reduction in the risk of HE recurrence). In keeping with this dramatic impact, rifaximin use was also associated with a reduction in hospitalizations for HE, with a 31% reduction in all-cause hospitalization over the 6-month period of follow-up. Rifaximin was associated with a greater than 40% reduction in hospitalizations specifically for HE, revealing HE as the main cause of hospitalization in these patients. The benefits of this therapeutic approach are obvious and would also result in substantial savings in overall healthcare cost related to HE.

Sigal and associates provide further analysis of RFHE3001, considering patient factors that independently predicted HE breakthrough in the rifaximin versus placebo populations. A number of factors potentially predictive of breakthrough were identified on the basis of a univariate regression analysis. These included the number of HE episodes in the 6 months prior to screening; the presence or absence of a transjugular portosystemic shunt (TIPS); the patient's age; the duration of remission at screening; and the patient's MELD score. On multivariate analysis, the authors showed that only age and baseline MELD score were significantly associated with HE breakthrough.

Thus, the authors rigorously address the question of whether any of these factors, perhaps through an imbalance in randomization, could have disproportionately affected outcomes of the trial. When outcomes analysis was adjusted for all of the factors listed above, the preventive effect of rifaximin increased from 58% to 60%, effectively ruling out these potentially confounding variables as influencing the trial outcome. It should be further noted that differences in the use of lactulose during the trial have also been addressed carefully, with no difference seen between the rifaximin and placebo arms in terms of either baseline lactulose use or lactulose use during the trial. From a clinical viewpoint, this analysis confirms that patients who are older and have more advanced liver disease are more likely to have recurrent HE episodes. The number of previous HE episodes, presence of TIPS, and duration of remission at screening should also be considered as potential risk factors, while other studies have also pointed to diabetes mellitus as a potential risk factor for HE recurrence.

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Biologic Therapies for Crohn's Disease

751f One Year Data from the SONIC Study: A Randomized, Double-Blind Trial Comparing Infliximab and Infliximab Plus Azathioprine to Azathioprine in Patients with Crohn's Disease Naïve to Immunomodulators and Biologic Therapy[1]

WJ Sandborn, PJ Rutgeerts, W Reinisch, GJ Mantzaris, A Kornbluth, D Rachmilewitz, S Lichtiger, GR D'Haens, CJ van der Woude, R Diamond, D Broussard, KL Tang, J-F Colombel

The anti-tumor necrosis factor alpha (TNF) monoclonal antibody infliximab is a frequently used and effective treatment for moderate-to-severe Crohn's disease (CD), although its efficacy compared to or in combination with immunomodulators has not yet been determined.[2] Azathioprine is often employed prior to the use of infliximab in the traditional step-up strategy of CD therapy, although it is possible that initiating azathioprine therapy earlier in treatment may help to alter the course of CD.[3,4] To determine the safety and efficacy of infliximab and azathioprine in combination and compared with each other as monotherapy, Sandborn and colleagues conducted the Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease (SONIC) trial.[1]

SONIC was a multicenter, double-blind, active-controlled phase III study comparing infliximab monotherapy (5 mg/kg), azathioprine monotherapy (2.5 mg/kg), and infliximab (5 mg/kg) combined with azathioprine (2.5 mg/kg). Oral azathioprine was given daily, and infliximab was administered by infusion at weeks 0, 2, and 6, followed by maintenance infusions every 8 weeks. A total of 508 moderate-to-severe CD patients with no prior history of immunosuppressive or biologic therapy were randomized to the three treatment arms for 30 weeks. After completion, patients were given the option to continue in a blinded extension study through week 50. Final efficacy results were assessed at week 50.

The primary study endpoint, corticosteroid-free remission (defined by a CD Activity Index [CDAI] score <150) at week 26, was significantly different among the three treatment groups. Significantly more patients in the combination arm (56.8%) achieved corticosteroid-free remission compared with both the infliximab monotherapy (44.4%) and single-agent azathioprine (30.0%) arms (P<.001 for combination versus azathioprine only; P=.006 for infliximab only versus azathioprine only; P=.022 for combination vs infliximab only).

At the completion of the initial portion of the study, a total of 55% of patients entered the blinded extension study. Of these patients enrolled in the extension study, a significantly higher proportion of patients in the combination arm (72.2%) were in corticosteroid-free remission at week 50 compared with the infliximab monotherapy (60.8%) arm and single-agent azathioprine (54.7%) arm (P=.010 for combination vs azathioprine only; P=.324 for infliximab only vs azathioprine only; P=.065 for combination vs infliximab monotherapy). Overall, when it was assumed that patients not entering the extension study had not achieved remission by week 50, the proportion of patients in corticosteroid-free remission at week 50 was 46.2%, 34.9%, and 24.1% for the combination arm, infliximab monotherapy arm, and single-agent azathioprine arm, respectively (P<.001 for combination vs azathioprine only; P=.028 for infliximab only vs azathioprine only, P=.035 for combination vs infliximab only). There was no significant difference in the incidence of serious infections among the treatment groups, and no new opportunistic infections, malignancies, or deaths occurred during the extension study.

Sandborn and colleagues concluded that both infliximab regimens were more likely than azathioprine to achieve long-term steroid-free remission, although the combination of infliximab with azathioprine was superior to infliximab alone. No significant differences in adverse events were observed among the treatment arms.

751e Adalimumab Induces and Maintains Mucosal Healing in Patients with Moderate to Severe Ileocolonic Crohn's Disease—First Results of the EXTEND Trial[5]

P Rutgeerts, GR D'Haens, GA Van Assche, WJ Sandborn, DC Wolf, J-F Colombel, W Reinisch, K Geboes, M Khan, A Lazar, A Camez, PF Pollack

Adalimumab is a fully human monoclonal antibody directed against TNF. Multiple clinical studies have established the safety and efficacy of adalimumab to induce response and remission in CD patients.[6-9] Emerging

Table 1. Mucosal Outcomes at Weeks 12 and 52 Following Randomization to Either Adalimumab or Placebo Maintenance Therapy in the EXTEND Study

Outcome	Adalimumab Maintenance	Placebo Maintenance	*P* value
Complete mucosal healing, %			
Week 12*	27.4	13.1	.056
Week 12†	27.9	12.5	.046
Week 52*	24.2	0	<.001
CDEIS remission at week 52*, %	25	1.5	<.001
Mean change in SES-CD from baseline at week 52*	11.582	6.408	<.001

CDEIS=Crohn's disease endoscopic index of severity; SES-CD=simple endoscopic score for Crohn's disease
*Intent-to-treat population
†Per-protocol population

evidence suggests that in addition to clinical remission, mucosal healing may be an important determinant of long-term patient outcome.[10,11] Infliximab has been shown to induce mucosal healing in CD patients, an effect which was associated with improved long-term outcome and a decreased need for surgery.[12] In the EXTEND trial, Rutgeerts and colleagues assessed the efficacy of adalimumab for inducing mucosal healing in CD patients.[5]

The EXTEND study enrolled 135 patients with moderate-to-severe ileocolonic CD. The mean duration of CD was 10 years. At baseline, patients had a mean CDAI between 220 and 450 and a mucosal ulceration score of 2 or 3 for 1 or more colon segment (assessed using the Ulcerated Surface subscore of the Simple Endoscopic Score [SES] for CD).[13] The mean CDAI score was 320 and the mean CDEIS score was 19. A majority of patients (61%) had previous exposure to an anti-TNF□ therapy, 41% were receiving concomitant immunosuppressants, and 26% were receiving concomitant steroids. All patients initially received open-label adalimumab induction therapy (160 mg and 80 mg at weeks 0 and 2, respectively). At week 4, patients (n=129) were then randomized to receive adalimumab maintenance therapy (40 mg every other week) or placebo through week 52. At randomization, patients were stratified by whether or not they had experienced a decrease in CDAI of 70 points or more from baseline (CDAI-70 response). Starting at week 8, patients experiencing disease flares or other indications of no response could receive open-label adalimumab (40 mg every other week); those who experienced continued flares could increase the open-label adalimumab dosage to every week. The primary endpoint of the study was the proportion of patients healing at week 12. The degree of mucosal healing was determined by colonoscopy at baseline, week 12, and week 52 or upon early termination. Patients who switched to open-label adalimumab were additionally assessed by colonoscopy during weeks 8–12 prior to switching and at the time of the switch to adalimumab, if after week 12. Secondary study endpoints at weeks 12 and 52 included clinical remission (defined as a CDAI <150), a CD Endoscopic Index of Severity (CDEIS) of 4 or less, and mean change in SES for CD.

At week 12 in the intent-to-treat analysis, significantly more patients who received adalimumab maintenance therapy achieved complete mucosal healing compared with patients who received placebo (27.4% vs 13.1%, *P*=.056; Table 1). A protocol yielded similar results (27.9% versus 12.5%, *P*=.046). Adalimumab maintenance therapy was also found to be significantly superior to placebo for inducing complete mucosal healing at week 52 (24.2% vs 0%, *P*<.001) and remission by CDEIS at week 52 (25% vs 1.5%, *P*<.001). Patients who continued adalimumab maintenance treatment showed a substantial reduction in SES-CD from baseline (11.582 vs 6.408, *P*<.001). Adalimumab maintenance therapy also resulted in improved rates of clinical remission at both week 12 (46.9% vs 27.7%, *P*<.05) and week 52 (32.8% vs 9.2%, *P*<.05). The incidence of serious adverse events was similar between the two treatment groups.

Based on these data, the investigators concluded that adalimumab maintenance therapy resulted in an improved rate of complete mucosal healing compared with placebo. Importantly, this difference was observed as early as week 12, and maintained over 1 year. The extent of mucosal healing was determined by colonoscopy and confirmed through multiple secondary endpoints including CDEIS and SES for CD.

S1144 Adalimumab Induces Sustained Fistula Healing in Both Anti-TNF-Naïve and Anti-TNF-Experienced Patients with Crohn's Disease: The CARE Trial[14]

R Lofberg, E Louis, W Reinisch, M Kron, A Camez, A Robinson, PF Pollack

Adalimumab is effective in the induction and maintenance of CD remission both in infliximab-naïve patients and in patients with prior infliximab exposure.[6,15] Subgroup analysis of the Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM) study suggested that adalimumab treatment

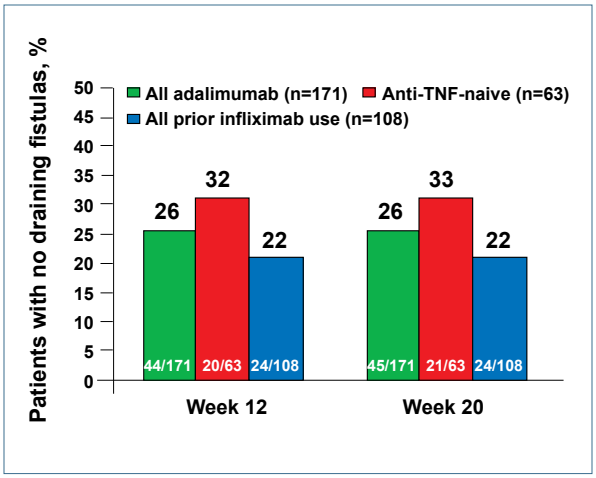

Figure 5. Complete fistula healing stratified by anti-TNF history: NRI analysis.*

*Results at week 20 were compared with the Fisher exact test; there were no differences between the anti-TNF-naive and infliximab-experienced subgroups.

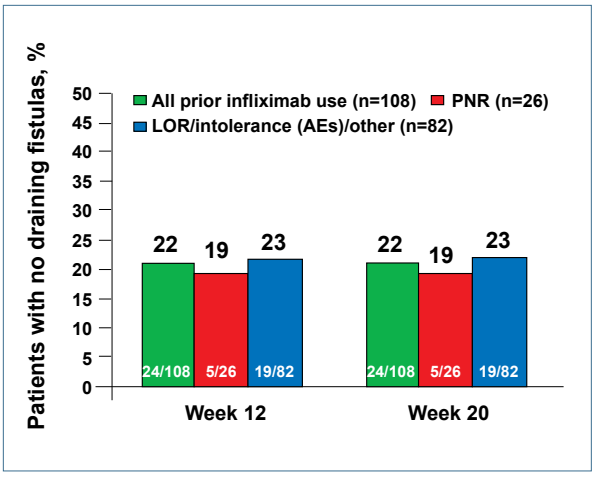

Figure 6. Complete fistula healing in patients with prior infliximab therapy by reason for discontinuation of infliximb: NRI analysis.*

*Results at week 20 were compared with the Fisher exact test; there were no differences between the 2 infliximab subgroups.

resulted in complete fistula closure with a duration of up to 3 years; this finding was confirmed in the open-label extension study Additional Long-Term Dosing with Humira to Evaluate Sustained Remission and Efficacy in CD (ADHERE). Lofberg and colleagues sought to determine if patients who had previously failed conventional therapy (both anti-TNF□-naïve and -experienced) also benefited from adalimumab-induced sustained fistula healing.[14]

The Crohn's Patients Treated with Adalimumab: Results of a Safety and Efficacy Study (CARE) trial was a European multicenter, open-label, single-arm trial. A total of 945 enrolled patients with moderate-to-severe CD were administered adalimumab induction therapy (160 mg and 80 mg at weeks 0 and 2, respectively) followed by adalimumab maintenance therapy beginning at week 4 (40 mg every other week). Treatment was continued for a minimum of 20 weeks. After week 12, patients experiencing flares or with no response were given the option to receive adalimumab maintenance treatment weekly. All patients had previously failed to respond to conventional CD therapy, were either infliximab-naïve or infliximab-experienced, with a Harvey-Bradshaw Index (HBI) score of 7 or greater. At physical examination, the number of cutaneous fistulas determined to be draining with gentle compression were counted, and the rate of complete fistula healing (no draining fistulas) and fistula response (≥50% reduction in the number of draining fistulas) was determined.

At baseline, 18% of patients (n=171) had 1 or more draining fistula; this group of patients was separately analyzed and classified into patients who were infliximab-naïve (n=63) or infliximab-experienced (n=108). Although patient characteristics were relatively similar between these groups, infliximab-experienced patients were more likely to be female and had a longer duration of disease. Of the 108 infliximab-experienced patients, 24% had exhibited a primary nonresponse to infliximab.

After 12 weeks of adalimumab therapy, complete fistula healing was present in approximately one-quarter (26%) of patients with 1 fistula or more (Figure 5). Results were similar, irrespective of prior treatment status (32% naive vs 22% infliximab-experienced). The same was true at week 20 as well (26%, 33%, 22% for overall, infliximab-naïve, and infliximab-experienced patients, respectively). The rates of complete fistula healing were also not significantly affected by the reason for infliximab discontinuation among infliximab-experienced patients (Figure 6).

Similar results were observed for the rate of fistula response (≥50% reduction in the number of draining fistulas) following adalimumab therapy. At week 12, 30% of treated patients who had 1 or more fistula at baseline achieved a fistula response; this rate was not significantly different among the infliximab-naïve and infliximab-experienced patient subgroups (37% and 26%, respectively). Similar rates of fistula response were also observed at week 20 (31%, 38%, and 27% for all patients, infliximab-

naïve, and infliximab-experienced patients, respectively). The rate of fistula response was not significantly affected by the reason for discontinuation of infliximab among the infliximab-experienced patient subgroup.

In the overall CARE study population, the rate of serious adverse events was 19%. The safety profile among the subgroup of patients with fistulas was representative of the overall population, with 42.1% of patients reporting an adverse event that was at least possibly related to the study drug. The rate of serious adverse events among this patient subgroup was 19.3%, and 12.3% of patients experienced an adverse event that led to the discontinuation of the study drug.

Lofberg and colleagues concluded that in the subgroup of patients from the CARE trial who had 1 or more draining fistula at baseline, adalimumab treatment resulted in clinically meaningful rates of complete fistula healing by week 12. Importantly, these results were durable, lasting until the assessment at week 20. This benefit of adalimumab occurred regardless of whether patients were infliximab-naïve or infliximab-experienced.

S1127 Infliximab in Crohn's Disease: Long Term Durability Experience[16]

M Dibb, K Kemp, C Johnson, AJ Makin, A Watson, S Campbell

Although infliximab has been shown effective in short-term clinical trials for both induction and maintenance of response and remission in CD, less is known regarding the long-term durability of therapy

Dibb and colleagues evaluated 106 CD patients who had received treatment with infliximab between October 1999 and October 2008. The investigators created a database of patients, which recorded demographic characteristics, smoking status, the concomitant use of immunosuppressant agents, observations regarding disease type and anatomy, and assessments of adverse events and time to loss of response. Loss of response to infliximab was defined as a requirement to either reduce the dosing interval or to increase the dose in order to recapture response. The median patient age was 39 years (range: 17–79 years). The extent of CD involvement represented included ileal (37.7%), colonic (24.5%), ileocolonic (31.3%), and upper gastrointestinal (6.6%). Approximately half (48.1%) of the patients had perianal involvement. An induction regimen of infliximab was administered at 0, 2, and 6 weeks. During induction, 18.9% of patients discontinued infliximab due to either the occurrence of a serious adverse event, lack of response, or requirement for surgery. Among the remaining patients, most received scheduled infliximab maintenance therapy (q 8 weekly or q 12 weekly), although 13.2% received infliximab on an episodic basis. The mean duration of infliximab therapy was 19.7 months (range: 2–93 months).

No significant difference in the loss of response to infliximab was observed between patients who received 8-weekly doses versus 12-weekly doses of maintenance therapy. After a follow-up of 8 years, 16% of patients who had initially responded to infliximab were in remission. More patients without perianal involvement were in remission at 5 years compared with patients who had perianal involvement (44% versus 18%, P=.056). A response at 5 years was observed in a higher proportion of non-smokers compared with smokers (58.7% versus 31.6%), and no patients classified as ex-smokers had a response at 5 years (P=.007). Neither disease location nor age had a significant effect on the durability of infliximab response.

An allergic reaction to infliximab was recorded in 9.4% of patients, and 3.7% developed an infection requiring discontinuation of therapy. Dyspnea leading to infliximab discontinuation occurred in 2 patients, and depression in 1 patient led to discontinuation of the drug.

Dibb and colleagues concluded that after 8 years, only 16% of patients who had initially responded to infliximab were in remission. Perianal involvement and smoking increased the risk of poor long-term outcomes with infliximab therapy. The investigators also noted that due to the high proportion of patients who received concomitant treatment with immunosuppressant agents, the effect of these drugs on the durability of infliximab therapy could not be determined.

143 WELCOME: A Randomized, Double-Blind, Controlled Trial Comparing Certolizumab Pegol 400 Mg Every 2 Weeks with Every 4 Weeks for Maintenance of Response and Remission in Patients with Moderate to Severe Crohn's Disease with Secondary Failure to Infliximab[17]

WJ Sandborn, S Vermeire, GR D'Haens, J-F Colombel, RN Fedorak, ME Spehlmann, DC Wolf, MT Abreu, K Mitchev, C Jamoul, PJ Rutgeerts

Approximately 40% of CD patients who initially responds to anti-TNF□ therapy either lose response or experience immunologically mediated adverse reactions with continued use. Certolizumab pegol, a TNF□-targeting pegylated humanized Fab' fragment with a unique mechanism, may provide an alternative for these patients.[18] Importantly, certolizumab pegol has been shown to be effective in the maintenance of response and remission among both patients who were infliximab-naïve or infliximab-experienced.[19] Here, Sandborn and colleagues evaluated two

Table 2. Clinical Outcome According to Certolizumab Pegol Treatment Schedule in the WELCOME Study

Outcome	Certolizumab Pegol Schedule	
	Every 2 Weeks (n=161)	Every 4 Weeks (n=168)
Clinical response, %		
≥100 point decrease in CDAI	36.6	39.9
≥70 point decrease in CDAI	41.0	42.9
Clinical remission, %		
≤150 point decrease in CDAI	30.4	29.2

CDAI=Crohn's disease activity index

dose schedules of certolizumab pegol in CD patients who had previously lost response or developed hypersensitivity to infliximab.[17]

The WELCOME study was a multicenter phase IIIb clinical trial comprised of a 6 week open-label induction regimen followed by a double-blind maintenance regimen. Eligible patients had moderate-to-severe CD, a CDAI score between 220 and 450, and a history of infliximab failure (either due to lost response or the development of hypersensitivity reactions). A total of 539 patients received certolizumab pegol (400 mg) at weeks 0, 2, and 4 as part of the open-label induction phase. Clinical response, defined as a decrease in CDAI of 100 or more points from baseline, was assessed at week 6; nonresponders were withdrawn from the study. Of the 62.0% (n=334) of responding patients, 329 were randomized to the maintenance phase of the trial to receive certolizumab pegol (400 mg) either every 2 weeks or every 4 weeks. Treatment was continued through week 24. Remission was defined by a CDAI score of 150 points or less.

No significant difference in either the rates of response or remission was observed between the two certolizumab pegol schedule groups (Table 2). The rate of patients achieving a CDAI-100 response (≥100 point decrease in CDAI from baseline) was similar for the every-2-week and every-4-week groups (36.6% versus 39.9%). The rate of patients achieving a CDAI-70 response was also similar between the two groups (41.0% versus 42.9%). The proportion of patients achieving remission was also not significantly different between the every-2-week and every-4-week treatment groups (30.4% versus 29.2%).

Sandborn and colleagues noted that over half (62.0%) of patients who were refractory or resistant to infliximab responded to the open-label induction treatment with certolizumab pegol. For responding patients, a maintenance regimen schedule every 4 weeks was similar in efficacy to every 2 weeks.

S1044 Natalizumab Use in Patients with Crohn's Disease and Relapsing Multiple Sclerosis: Updated Utilization and Safety Results from the TOUCH™ Prescribing Program, the Pregnancy Registry, and the Inform and TYGRIS Studies[20]

BE Sands, M Kooijmans, C Bozic, A Hamdy, E Kouchakji, GS Hogge

The alpha-4-integrin receptor antagonist natalizumab is currently approved to treat CD. However, natalizumab therapy is associated with the development of progressive multifocal leukoencephalopathy (PML), an opportunistic infection related to the presence of JC virus. Accordingly, natalizumab was removed from the US market, but was recently returned under a special prescription program requiring careful safety monitoring and data collection. Several programs have been established to monitor the safety and efficacy of natalizumab. The Tysabri Outreach: Unified Commitment to Health (TOUCH™) program is a mandatory prescription program in the United States that ensures patients are properly informed regarding the risks and benefits of natalizumab, as well as appropriate use of the drug.[21] TOUCH is specifically designed to monitor patients for signs and symptoms of PML or other serious opportunistic infections. The CD Investigating Natalizumab through Further Observational Research and Monitoring (CD-INFORM) program is a voluntary study within the United States, with the goal of collecting data regarding patient history, efficacy (assessed by the HBI), health-related quality of life, and serious adverse events in CD patients receiving natalizumab. The Tysabri Global Observation Program in Safety (TYGRIS) is a global voluntary observational study evaluating the long-term safety of natalizumab in patients with multiple sclerosis (MS). A pregnancy registry has also been initiated. Here, Sands and colleagues reported updated efficacy and safety data on natalizumab from these programs.[20]

Through September 2008, approximately 48,000 patients (CD and MS) have been exposed to natalizumab through either a clinical study or post-marketing setting. The vast majority of these (~95%) were MS patients. Of over 35,500 patients currently receiving natalizumab, 231 were being treated for CD. As of November 2008, 3 cases (all MS patients) of PML had been confirmed

among patients receiving natalizumab in the post-marketing setting; all 3 of these patients were alive at the time of preparation of this abstract.

A total of 64 women had been prospectively enrolled in the pregnancy registry at the time of this abstract; 27 healthy babies were delivered to 27 patients with no report of natalizumab-associated birth defects.

Sands and colleagues concluded that according to the cumulative data available through each of these registries, the safety of natalizumab is similar to that observed during clinical trials.

140 Direct and Indirect Economic Burdens and Impact on Salary Growth of Moderate to Severe Crohn's Disease[22]

EV Loftus, A Guerin, M Tsaneva, AP Yu, J Chao, P Mulani

CD has a large economic burden. One previous study estimated that annual medical costs associated with CD were significantly higher than a matched comparison group ($18,963 versus $5,300).[23] Another recent study reported that patients with active disease experienced medical costs that were 3- to 9-fold higher than those experienced by patients in remission.[24] Loftus and colleagues investigated the direct (medical and pharmaceutical costs) and indirect (disability and absenteeism costs) economic burden of CD, and assessed the impact of CD on salary growth.[22]

The investigators obtained information from a database of beneficiaries compiled from 40 large self-insured employers in the United States between 1996 and 2007. Active employees with moderate-to-severe CD were identified and included if they had a record of receiving treatment (immunosuppressant agents, corticosteroids, or biologic therapy) within 6 months of a diagnosis of CD. Each CD patient was matched to 3 control employees without CD. Patient enrollment into this study was continued on a rolling basis for 1 year. All cost estimations are in 2007 US dollars.

A total of 1,279 CD patients and 3,837 individuals without CD were included. Unadjusted direct medical costs were nearly 10-fold higher among CD patients ($20,206 versus $2,911). Likewise, unadjusted indirect costs were also higher in patients than in controls ($3,921 versus $1,045). After adjustment, the total incremental direct medical costs for patients with CD was $15,775 per year ($P<.001$) and the total incremental indirect costs for these patients was $1,886 per year ($P<.001$).

The salary growth rate was determined at a compounded annualized rate, and adjusted for inflation. Employees with CD experienced a 0.23% lower annual salary growth rate compared to their counterparts without CD ($P<.001$). For employees starting at an annual salary of $60,000, this translated into a loss of $2076 in income over 5 years.

The investigators concluded that CD was associated with an important economic burden with significant increases in both direct and indirect adjusted medical costs, in comparison to unaffected controls. Additionally, CD patients have a lower annual salary growth, suggesting that career progression was limited by the disease.

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Commentary

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The efficacy and safety of combined immunosuppressive and TNF antagonist therapy relative to TNF antagonist monotherapy is a highly controversial topic in the management of Crohn's disease (CD). Shifting opinions on this subject have resulted from a lack of strong data supporting the benefit of combination therapy.

In contrast, combined therapy with methotrexate and an anti-TNF is a standard of care in rheumatoid arthritis treatment, because the combination is synergistically effective and methotrexate is protective against the formation of anti-drug antibodies. Furthermore, a biologic rationale for combination therapy has been documented. In vitro data suggest that both azathioprine and methotrexate increase lymphocyte apoptosis, which is one of the putative mechanisms of action of TNF antagonists. However, given the lack of empiric data to support these concepts in CD and widespread concerns regarding the possibility of increased toxicity, particularly opportunistic infections, considerable resistance to the use of combination therapy exists among clinicians. Furthermore, during the past 4 years, concerns regarding rare cases of hepatosplenic T-cell lymphoma in young patients have resulted in increased use of TNF antagonist monotherapy at many IBD centers.

Given this situation, data from the landmark SONIC trial are particularly helpful. SONIC has clearly shown that combination therapy is more effective than monotherapy with either azathioprine or infliximab. Corticosteroid-free remission rates were substantially higher for the combination at both 6-month and 1-year time points. The relative magnitude of the effect suggests an additive treatment effect, in distinction from true synergy. In addition, subgroup analyses provide further important information regarding optimal treatment strategies. The SONIC investigators assessed all patients at the baseline visit for active inflammation, by colonoscopy and measurement of the serum concentration of C-reactive protein (CRP). Patients with active ulcers in the colon and/or an elevated concentration of CRP showed an even greater benefit from combination therapy than was observed in the intent-to-treat analysis. Patients without these characteristics showed no benefit over azathioprine monotherapy. These findings generate two important conclusions. First, the sickest patients are the most appropriate candidates for combination therapy. Second, objective assessment for active inflammation is mandatory before initiating combination therapy.

Finally, SONIC provides important information regarding the risk of serious infection in patients receiving combination therapy. In contrast to the widely held belief that combination therapy is associated with a greater risk of serious infection than monotherapy with either azathioprine or infliximab, SONIC patients who received combination therapy were no more likely to develop infectious complications than those assigned to either monotherapy arm. In summary, SONIC provides strong evidence for the superiority of combination therapy. These results should change clinical practice.

Mucosal healing is a goal of therapy that has received increased attention in recent years. Conceptually, if we are to favorably alter the natural history of IBD, mucosal ulceration must be both treated and prevented. Our traditional treatment approach has relied on evaluating symptoms to guide therapy. However, corticosteroids control symptoms remarkably well but their use is not associated with high rates of complete mucosal healing or any change in longterm outcomes. It is possible that if mucosal healing becomes a primary treatment goal, higher rates of complication-free survival and reduced rates of hospitalization might be expected. Data do exist to support this notion. For example, studies in at least two of the three currently approved anti-TNF therapies have demonstrated that treatment decreases rates of hospitalization and surgery. The next step in the validation of this strategy would be to confirm the link between mucosal healing and prevention of those same major complications.

Data from the EXTEND trial do not make this link explicit but the trial does provide compelling evidence that adalimumab can heal the colonic mucosa. As with all mucosal healing studies, interpretation of the data is complicated by our lack of insight into the clinical significance of the outcomes measured, as well as the heterogeneity of disease severity among the patients studied. Although only borderline statistical significance was observed for the primary outcome measure, all of the secondary endpoints in EXTEND were statistically significant. Based on the consistency of these data, we can conclude that adalimumab is effective in healing the mucosa. Although it is tempting to compare the results of EXTEND to other mucosal healing trials of TNF antagonists, such contrasts should be discouraged because of differences in trial design, patient populations, outcome measures, and methods of analysis.

The CARE trial was an open-label experience with adalimumab therapy. Because the study assessed a large number of patients, it was possible to examine a subgroup of participants with fistulizing CD. Although the study was not controlled, randomized, or blinded, the authors did evaluate a relatively large number of both infliximab-naïve and infliximab-experienced patients. The results show a benefit for adalimumab administration in closing fistulas. Sub-group analysis from the CHARM trial also support the use of adalimumab in these patients.

Dibb and colleagues preformed an open-label, retrospective review of the long-term outcomes of infliximab therapy. In this real-world experience, the proportion of patients with long-term, steroid-free remission was low. Although the results call into question the durability of response with TNF antagonists, they are difficult to interpret because of the inability of the retrospective design to control for potential confounding factors. For example, the abstract provides no information on why patients stopped infliximab. Was it due to patient or clinician preference, economic reasons, lack of efficacy, or poor tolerability? These are all reasons why patients discontinue maintenance therapy. For this reason, the authors' data do not provide definitive proof that TNF antagonists have poor long-term efficacy. Furthermore, these results are in direct contrast to prospectively collected observational data from Rutgeerts and colleagues that were recently published in *Inflammatory Bowel Disease*. The discordance between the two studies underscores the need for further long-term study addressing this question.

The WELCOME study evaluated the efficacy of two different dose regimens of certolizumab pegol in the treatment of patients with a secondary loss of response or intolerance to infliximab. Following a standard induction regimen of certolizumab pegol, responding patients were randomly assigned to an intense regimen consisting of 400 mg of drug every 2 weeks or conventional once-monthly dosing. In the open-label induction phase of the trial, a very high response rate (62%) was observed in a patient population that had, for the most part, lost response to infliximab. This is an important finding, suggesting that certolizumab pegol is a valuable treatment option for an important clinical problem. Although the more intense dosing schedule in the maintenance phase did not translate into greater efficacy as a maintenance therapy, neither did it increase the rate of adverse events. This finding provides further reassurance for patients who are administered overlapping anti-TNF regimens due to drug failure, because a strong relationship between adverse events and drug exposure was not demonstrated.

Sands and associates evaluated safety issues associated with the alpha-4 integrin antagonist natalizumab. Since the introduction of natalizumab therapy for CD, its use has been restricted to patients who are refractory to other forms of medical therapy, due to concern for the risk of developing progressive multifocal leukoencephalopathy (PML). This abstract presents data from two large post-marketing surveillance programs that are mandated by regulatory authorities in both the United States and Europe. Both multiple sclerosis and CD patients were evaluated.

These are important data because gastroenterologists have been reluctant to utilize natalizumab, due to the perception that it is less safe than other biologics. The current data suggest that this is not the case and that the overall rates of serious infectious complications are similar to those with TNF antagonists. The cases of PML observed have been detected early in the course of the disease and pheresis therapy to remove the drug from the blood has been initiated. These measures seem to have improved the outcome of patients who developed this serious complication. However, the stigma of neurological complications from PML has greatly influenced prescribing behavior. Whether this is appropriate remains an open question.

The final study addresses the economic burden and impact of CD. This information will be of interest to both employers and third party payers. The unique aspect of this abstract is the data regarding the effect of CD on patients' salary growth rate, a question that has never been formally studied before. The authors have demonstrated that patients with the disease have a slower rate of growth in annual salary and are likely disadvantaged in the work force.

Overall, these studies reflect many of the current opportunities and challenges associated with the new era of biologic therapy for CD. Multiple new biologic agents are on the horizon and hold out the promise of better long-term outcomes for our patients. Future research will continue to focus on strategies that will ultimately alter the natural history of the disease.

Suggested Reading

Schnitzler F, Fidder H, Ferrante M, Noman M, Arijs I, et al. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. *Inflamm Bowel Dis.* 2009 Apr 1. [Epub ahead of print]

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Emerging Issues in Gastroenterology and Hepatology

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

1. Which of the following statements best describes the findings regarding small intestinal bacterial overgrowth (SIBO) in HE from a presentation by Weisberg and colleagues?

   A. SIBO does not occur at an increased frequency among patients with hepatitis C virus-associated cirrhosis.
   B. SIBO occurs with a high frequency among patients with hepatitis C virus-associated cirrhosis, but decreases with increasing presence and severity of HE.
   C. SIBO occurs with a high frequency among patients with hepatitis C virus-associated cirrhosis, and increases with increasing presence and severity of HE.
   D. SIBO occurs at a low frequency among patients with hepatitis C virus-associated cirrhosis, but increases with increasing presence and severity of HE.

2. A presentation by Bajaj and colleagues reported what percentage of recurrent episodes of HE were due to misuse of lactulose (either noncompliance or misuse)?

   A. 8% B. 48% C. 70% D. 90%

3. In a subanalysis of the RFHE3001 trial conducted by Neff and colleagues, what effect did rifaximin treatment have on the secondary endpoint of time to first HE-related hospitalization?

   A. Significantly fewer HE-related hospitalizations were reported in the rifaximin group compared with the placebo group.
   B. Significantly more HE-related hospitalizations were reported in the rifaximin group compared with the placebo group.
   C. There was no change in the number of HE-related hospitalizations reported in the rifaximin group compared with the placebo group.
   D. Although rifaximin initially resulted in fewer HE-related hospitalizations, there was no change compared with the placebo group after 6 months.

4. In a subanalysis of the RFHE3001 trial conducted by Sigal and colleagues, which of the following factors was NOT found to independently significantly predict breakthrough HE episodes?

   A. Age
   B. Presence or absence of TIPS
   C. Baseline MELD score
   D. Presence of diabetes at baseline

5. All of the following statements correctly describes the findings from the SONIC trial, reported by Sandborn and colleagues, EXCEPT:

   A. Both infliximab regimens used (infliximab monotherapy and infliximab plus azathioprine) were more likely than single-agent azathioprine to achieve long-term corticosteroid-free remission, although the combination was superior.
   B. At week 26, significantly more patients in the infliximab plus azathioprine combination arm achieved corticosteroid-free remission compared with patients receiving infliximab monotherapy or single-agent azathioprine.
   C. Among patients continuing in the extension study, significantly more in the infliximab plus azathioprine arm were in corticosteroid-free remission at week 50 compared with those receiving monotherapy with infliximab or azathioprine.
   D. Patients in the infliximab plus azathioprine combination arm experienced a significantly higher rate of serious infections compared with the infliximab monotherapy or single-agent azathioprine arms.

6. The first results from the EXTEND trial, described by Rutgeerts and colleagues, demonstrated which of the following statements was TRUE?

   A. There was no significant difference in the proportion of patients achieving complete mucosal healing between the adalimumab and placebo arms at either week 12 or week 52.
   B. Significantly more patients in the adalimumab arm compared with the placebo arm achieved complete mucosal healing at both week 12 and week 52.
   C. Although significantly more patients in the adalimumab arm compared with the placebo arm achieved complete mucosal healing at week 12, this effect was not maintained at week 52.
   D. Although there was initially no significant difference in the proportion of patients achieving complete mucosal healing between the adalimumab and placebo arms at week 12, more patients in the adalimumab arm achieved this endpoint at week 52.

7. Which of the following statements correctly describes results from the CARE study, reported by Lofberg and colleagues?

   A. The rate of adalimumab-induced complete fistula healing was significantly lowered among patients previously treated with infliximab.
   B. The rate of adalimumab-induced complete fistula healing was significantly increased among patients previously treated with infliximab.
   C. The rate of adalimumab-induced complete fistula healing was only significantly lowered among patients who previously had a primary nonresponse to infliximab.
   D. The rate of adalimumab-induced complete fistula healing was not significantly affected by prior treatment with infliximab.

8. In a study reported by Dibb and colleagues, what proportion of patients who had initially responded to infliximab were in remission after a follow-up of 8 years?

   A. 16% B. 34% C. 57% D. 79%

9. True or False? The WELCOME study, reported by Sandborn and colleagues, demonstrated there was no significant difference in either the rates of response or remission between the two certolizumab pegol schedule groups (every 2 weeks versus every 4 weeks).

   A. True B. False

10. In a cost analysis performed by Loftus and colleagues, the unadjusted direct medical costs for patients with CD was approximately _____ higher compared with individuals without CD.

    A. 2-fold
    B. 5-fold
    C. 10-fold
    D. 50-fold

Evaluation Form
Emerging Issues in Gastroenterology and Hepatology

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 answer the following questions by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Extent to Which Program Activities Met the Identified Objectives

After completing this activity, I am now better able to:

1. Describe the pathophysiology of hepatic encephalopathy (HE).	1	2	3	4	5
2. Discuss efficacy of current therapeutic options for HE.	1	2	3	4	5
3. Assess recent research into the evolving role of biologic therapies in the treatment of Crohn's disease.	1	2	3	4	5

Overall Effectiveness of the Activity

The content presented:

Was timely and will influence how I practice	1	2	3	4	5
Enhanced my current knowledge base	1	2	3	4	5
Addressed my most pressing questions	1	2	3	4	5
Provided new ideas or information I expect to use	1	2	3	4	5
Addressed competencies identified by my specialty	1	2	3	4	5
Avoided commercial bias or influence	1	2	3	4	5

Impact of the Activity

Name one thing you intend to change in your practice as a result of completing this activity.

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

Additional comments about this activity. _____

Follow-up

As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

☐ Yes, I would be interested in participating in a follow-up survey. ☐ No, I'm not interested in participating in a follow-up survey.

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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