GASTROENTEROLOGY & HEPATOLOGY
The Independent Peer-Reviewed Journal

A Special Meeting Review Edition | THE GASTRO & HEP REPORT | Fall 2014

Presentation summaries in:

Comprehensive Reports on the Latest Advances in Gastroenterology and Hepatology From:

Digestive Disease Week

May 3-6, 2014
Chicago, Illinois

The 49th Annual Meeting of the European Association for the Study of the Liver

April 9-13, 2014
London, United Kingdom

ON THE WEB:
gastroenterologyandhepatology.net

Indexed through the National Library of Medicine
(PubMed/Medline), PubMed Central (PMC), and EMBASE

Innovation in liver disease management

INTRODUCING...

FibroScan touch 502

FibroScan 502 Touch is NOW available in the US!

Using the patented Vibration Controlled Transient Elastography (VCTE™), the FibroScan 502 Touch, available exclusively through Sandhill Scientific, is the first noninvasive device indicated for use as an aid in the clinical management of patients with liver disease.

For more information or to speak with a sales representative, contact Sandhill Scientific at 800.468.4556 or fibroscan@sandhillsci.com.

DISTRIBUTED BY

SANDHILL scientific

MANUFACTURED BY

ECHOSENS

Sandhill Scientific, Inc • 9150 Commerce Center Circle, #500 • Highlands Ranch, CO 80129 USA
800.468.4556 • 303.470.7020 • Fax: 303.470.2975

GASTROENTEROLOGY & HEPATOLOGY

THE GASTRO & HEP REPORT

Comprehensive Reports on the Latest Advances in Gastroenterology and Hepatology From:

- Digestive Disease Week
  May 3-6, 2014 • Chicago, Illinois
- The 49th Annual Meeting of the European Association for the Study of the Liver
  April 9-13, 2014 • London, United Kingdom

Table of Contents

Indexed through the National Library of Medicine (PubMed/Medline), PubMed Central (PMC), and EMBASE

Presentations in Hepatology

SAPPHIRE-II: A Phase 3 Trial of a Novel 3-Drug Combination in Treatment-Experienced Adults With Hepatitis C Virus Genotype 1

The randomized, double-blind, placebo-controlled, phase 3 SAPPHIRE-II (A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 [ABT-450/R/ABT-267] and ABT-333 Co-Administered With Ribavirin [RBV] in Treatment-Experienced Adults With Genotype 1 Chronic Hepatitis C Virus [HCV] Infection) trial evaluated a drug combination designed to inhibit 3 points of the viral life cycle. It consisted of a single-tablet coformulation of the protease inhibitor ABT-450 (150 mg) with ritonavir (100 mg) as a booster, plus the nonstructural protein 5A (NS5A) inhibitor ombitasvir (25 mg) and the nonnucleoside, nonstructural protein 5B (NS5B) polymerase inhibitor dasabuvir (250 mg twice daily). The trial enrolled 394 patients with noncirrhotic, genotype 1 hepatitis C virus (HCV) previously treated with pegylated interferon-α and ribavirin who relapsed or demonstrated a partial or null response. The primary endpoint was sustained virologic response at week 12 (SVR12). The primary efficacy analysis compared the SVR12 rate in patients receiving the active regimen with the historical response rate observed in a similar group of patients who had received re-treatment with telaprevir and pegylated interferon-α plus ribavirin.

Dr Stefan Zeuzem of the J.W. Goethe University Hospital in Frankfurt, Germany presented results of the study at the 2014 meeting of the European Association for the Study of the Liver (EASL; Abstract O1). Approximately two-thirds of patients had fibrosis stage F0 or F1, approximately 90% of patients had the interleukin 28B (IL-28B) non-CC genotype, and nearly 60% of patients had HCV subtype 1a. Among the 297 evaluable patients treated with the active regimen, the SVR12 rate was 96.3% (95% CI, 94.2%-98.4%), which was superior to the historical control rate of 65%. SVR12 rates were 95.3% among the 86 patients with prior relapse, 100% among the 65 patients with a prior partial response, and 95.2% among the 146 patients who failed to respond to prior treatment (Figure 1). The HCV subgenotype did not significantly influence response rates. Although no virologic breakthroughs occurred for patients on active treatment, 7 of 297 patients (2.4%) relapsed at posttreatment week 2 (n=2), 4 (n=3), or 8 (n=2), and resistance-associated variants were detected in 5 of these patients.

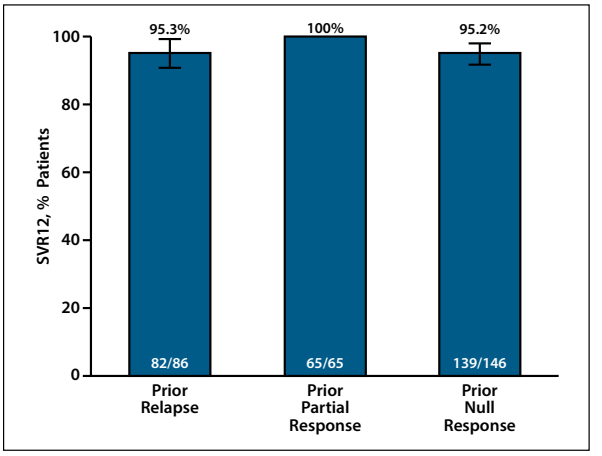


Figure 1. SVR12 rates in the SAPPHIRE-II trial. SAPPHIRE-II, A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/R/ABT-267) and ABT-333 Co-Administered With Ribavirin [RBV] in Treatment-Experienced Adults With Genotype 1 Chronic Hepatitis C Virus [HCV] Infection; SVR12, sustained virologic response at week 12. Adapted from Zeuzem S et al. EASL abstract O1. *J Hepatol.* 2014;60(suppl 1).

Pruritus was more frequent in patients receiving active treatment vs placebo (13.8% vs 5.2%; *P*=.03), and 3 patients in the active arm discontinued treatment owing to adverse events (AEs). Grade 3 hemoglobin values were reported in 0.3% of patients receiving active treatment.

Tenofovir Monotherapy Is an Option After Partial Response to Entecavir for Chronic Hepatitis B

Entecavir is one of the most effective antiviral drugs for treating chronic hepatitis B. However, limited alternative options exist for patients who respond poorly to the drug. At Digestive Disease Week 2014, Louis Lu, a medical student at the University of Michigan in Ann Arbor, Michigan, presented findings from a study examining outcomes from entecavir with or without tenofovir in patients with partial responses to entecavir monotherapy (Abstract 701). The retrospective cohort study included consecutive adult chronic hepatitis B patients from 7 medical practices in the United States. All patients had demonstrated partial responses to entecavir, defined as having detectable hepatitis B virus DNA at a concentration greater than 60 IU/mL at 12 months or more after

treatment with entecavir. Twenty-five patients were subsequently switched to tenofovir monotherapy, and 43 were switched to tenofovir plus entecavir. The study excluded patients who were treatment noncompliant or who developed resistance to entecavir.

Patients in the 2 groups had similar baseline characteristics, including age, sex, and hepatitis B e antigen status. Lamivudine resistance was documented in 4 patients in the tenofovir group and 1 patient in the combination group. Patients spent a median of 26 months on entecavir before switching to rescue therapy. Levels of hepatitis B virus DNA were slightly higher in the combination therapy group before the start of entecavir monotherapy (6.69 $\log_{10}$ IU/mL vs 7.71 $\log_{10}$ IU/mL; *P*=.01) and at the start of rescue therapy (3.10 $\log_{10}$ IU/mL vs 3.57 $\log_{10}$ IU/mL; *P*=.05). Levels of alanine aminotransferase were similar in the 2 groups before entecavir monotherapy and at the start of rescue therapy.

After 6 months of rescue therapy, viral suppression rates were 71% for patients who received tenofovir monotherapy and 83% for those who received tenofovir plus entecavir (*P*=.23). After 12 months of rescue therapy, viral suppression rates were nearly identical at 86% for tenofovir monotherapy and 84% with the combination (*P*=.85). Log-rank analysis showed no significant difference in the rates of viral suppression between the 2 rescue therapies. Based on multivariate analysis, combination therapy was not an independent predictor of viral suppression compared with tenofovir alone (odds ratio [OR], 1.31; *P*=.32). The researchers concluded that tenofovir monotherapy may represent a more convenient and cost-effective option over entecavir plus tenofovir in patients who respond poorly to entecavir alone.

Rifaximin Vs Lactulose in the Treatment of Minimal Hepatic Encephalopathy in Patients With Cirrhosis

Minimal hepatic encephalopathy (HE) has a significant impact on health-related quality of life (HRQOL) in patients with cirrhotic liver disease. A multicenter Indian and British team compared whether treatment with rifaximin or lactulose was associated with better neuropsychometric test performance and HRQOL in these patients. The findings of the team's prospective, randomized, single-blind, noninferiority trial were reported by Dr Omesh Goyal of the Dayanand Medical College and Hospital in Ludhiana, India at the 2014 EASL meeting (Abstract O169). The study tested 351 patients with cirrhotic liver disease for minimal HE, which was defined as a derangement beyond 2 standard deviations of normal on 2 neuropsychologic tests. The diagnosis was made in 112 patients (32%), who were randomized to receive 3 months of treatment with lactulose at dosages ranging from 30 mL/day to 120 mL/day (n=55) or rifaximin at a dosage of 1200 mg/day (n=57).

After 3 months of treatment, the rate of reversal of minimal HE was similar between the groups (67% for lactulose vs 65% for rifaximin). The AE profiles were also similar. HRQOL scores significantly improved in both groups and showed noninferiority of rifaximin in comparison with lactulose. Rifaximin, however, was more cost-effective than lactulose.

Hepatocellular Carcinoma in the Absence of Cirrhosis: Risk Factors and Treatment Trends

Nonalcoholic fatty liver disease (NAFLD) has recently been proposed as a possible risk factor for hepatocellular carcinoma. More than 1 in 10 patients with NAFLD-related hepatocellular carcinoma have no cirrhosis at presentation, and a lack of serologic disease markers makes it challenging to detect NAFLD in the general population. Moreover, there is a need for population-level studies examining the prevalence of risk factors for hepatocellular carcinoma without cirrhosis. At Digestive Disease Week 2014, Dr Sahil Mittal of the Baylor College of Medicine in Houston, Texas presented data from a study examining this issue in patients who developed hepatocellular carcinoma (Abstract Mo1035). Charts from Veterans Affairs hospitals in the United States were reviewed. NAFLD was diagnosed based on citation of histologic evidence of fatty liver infiltration or presence of metabolic syndrome without underlying cirrhosis. The presence of hepatitis B or HCV and alcohol use was documented.

Among the 1500 hepatocellular carcinoma patients identified, underlying risk factors included NAFLD in 120 patients (8%), HCV in 1013 (68%), and alcohol abuse in 286 (19%). Cirrhosis was absent in 42 patients (3%), highly improbable in 151 (10%), or definite in 1201 (80%); the diagnosis was unclear in 105 (7%). Hepatitis C infection was significantly more common in patients with cirrhosis (72%) than in those with probable cirrhosis (42%) or no cirrhosis (42%). NAFLD was more likely in patients harboring hepatocellular carcinoma without cirrhosis (OR, 3.1). At the time of hepatocellular carcinoma diagnosis, the proportion of patients with early-stage disease was 16% for those with a history of alcohol abuse, 6% for patients with underlying NAFLD, and 6% for those with HCV. A significantly higher proportion of patients with NAFLD had well-differentiated disease compared with the other 2 risk groups (*P*<.01), and NAFLD patients were less likely to be receiving specific treatment for their hepatocellular carcinoma (*P*<.01). Moreover, potentially curative treatments, including transplantation, resection, or ablation, were less common

in NAFLD patients (11%) compared with patients with HCV (22%) or history of alcohol abuse (13%; *P*<.01). Despite the differences in treatment, 1-year survival rates were similar among the patients (*P*=.09).

Rifaximin Plus Lactulose Vs Lactulose Alone for Overt Hepatic Encephalopathy

Rifaximin and lactulose are each used to reduce ammonia levels in HE. In a study reported at the 2014 EASL meeting, Dr Muzzaffar L. Gill of the Maroof International Hospital in Islamabad, Pakistan examined whether a combination of the 2 agents would improve outcome (Abstract P440). The study enrolled 200 patients with HE (30% with grade 2, 35% with grade 3, and 35% with grade 4). Patients were equally divided into 2 treatment groups: 1 group received rifaximin at a dosage of 550 mg twice daily and lactulose at a dose of 30 to 60 mL 2 to 3 times daily, and the other group received lactulose at the same dosage plus placebo. The treatment period was 10 days. The primary endpoint of the study was resolution of HE. The secondary endpoints were hospital stay and mortality.

The rate of complete resolution of HE was 75% in the combination group vs 45% in the lactulose monotherapy group (*P*=.005). The mortality rate was also lower in the combination group compared with the lactulose monotherapy group (20% vs 40%; *P*<.05). The combination group spent less time in the hospital; the average hospital stay was 4±2 days for the combination group vs 7±3 days in the lactulose monotherapy group (*P*=.005). The researchers concluded that the combination of rifaximin plus lactulose is more effective than lactulose alone in the treatment of HE.

Patients With Alcoholic Hepatitis Show Increased Intestinal Permeability and Increased Levels of Serum Lipopolysaccharides

Lipopolysaccharides are gut-derived, bacterial endotoxins that play a key role in the pathogenesis of alcoholic liver disease. Endotoxemia is necessary for the development of alcoholic liver disease. Chronic alcohol consumption (>100 g/day for years) can also lead to alcoholic hepatitis. Alcoholic liver disease is thought to arise from a defective intestinal barrier that allows lipopolysaccharides to enter the systemic circulation, leading to an inflammatory response in the liver. In a research forum at Digestive Disease Week 2014, Dr George Holman of the University of New Mexico School of Medicine presented results of a study examining the relationship between a defective intestinal barrier and endotoxemia (Abstract 39). In addition to examining whether patients with alcoholic hepatitis have increased intestinal permeability, the ongoing, prospective, case-control study is assessing the relationship between altered intestinal permeability and levels of lipopolysaccharide. The researchers are measuring levels of lactulose and mannitol in the urine to determine intestinal permeability, levels of serum lipopolysaccharide, and levels of IL-6 and tumor necrosis factor α (TNF-α) to determine inflammation.

The study evaluated 22 alcoholic hepatitis patients and 33 healthy controls for intestinal permeability. Lactulose excretion was 3 times higher in alcoholic hepatitis patients compared with controls (*P*=.001). However, mannitol excretion was decreased in alcoholic hepatitis patients (9.0%±1.8% vs 14.8%±1.0%; *P*=.008). Intestinal permeability, as evidenced by the lactulose/mannitol ratio, was 8-fold higher in alcoholic hepatitis patients (*P*=.002). Alcoholic hepatitis patients also exhibited significantly higher levels of serum lipopolysaccharide (671±158 pg/mL vs 63±11 pg/mL; *P*=.001). The correlation between intestinal permeability and serum lipopolysaccharide levels was demonstrated by a plot of the 2 factors that showed a robust, linear correlation (*r*=.98). Consistent with the increased serum levels of lipopolysaccharides, alcoholic hepatitis patients also exhibited significantly elevated levels of the proinflammatory cytokines IL-6 (72±15 pg/mL vs 2.5±0.4 pg/mL; *P*=.0003) and TNF-α (16.6±3.4 pg/mL vs 8.8±1.3 pg/mL; *P*=.045) compared with controls. Dr Holman and colleagues concluded that the higher intestinal permeability and serum levels of lipopolysaccharides in alcoholic hepatitis patients may lead to increased endotoxemia.

Once-Daily Simeprevir With Peginterferon/ Ribavirin in Patients With Chronic Hepatitis C Genotype 4

The open-label, multicenter, single-arm, phase 3 RESTORE (An Open-Label, Single-Arm Phase III Study to Evaluate the Efficacy, Safety and Tolerability of TMC435 in Combination With PegIFN Alfa-2a [Pegasys] and Ribavirin [Copegus] in Treatment-Naïve or Treatment-Experienced, Chronic Hepatitis C Virus Genotype-4 Infected Subjects) trial evaluated the safety and efficacy of the investigational HCV NS3/4A protease inhibitor simeprevir in combination with pegylated interferon-α and ribavirin in patients with chronic HCV genotype 4 infection and compensated liver disease. Dr Christopher Moreno of the Université Libre de Bruxelles in Brussels, Belgium presented results at the 2014 EASL meeting (Abstract 1319). The median age of patients was 49 years, and 7.5% had the *IL-28B* CC genotype. Metavir fibrosis stage F3 or F4 was observed in 14% and 29% of patients, respectively. All patients received simeprevir (150 mg/day) during weeks 1 to 12. All patients

also received pegylated interferon-α (180 µg weekly) and ribavirin based on weight (1000-1200 mg/day) during weeks 1 to 24. For previously untreated patients and prior relapsers, treatment was halted after 24 weeks if they met the response-guided therapy criteria of undetectable HCV RNA at treatment week 12. Patients with detectable HCV RNA at treatment week 12, as well as all prior null or partial responders, received the interferon/ribavirin regimen until treatment week 48.

By week 24, treatment was completed in 88.6% of treatment-naive patients and 90.9% of prior relapsers. SVR12 rates were 65.4% for the entire study population of 107 patients, 82.9% among the 35 treatment-naive patients, 86.4% for the 22 prior relapsers, 60.0% for the 10 prior partial responders, and 40.0% for the 40 prior null responders.

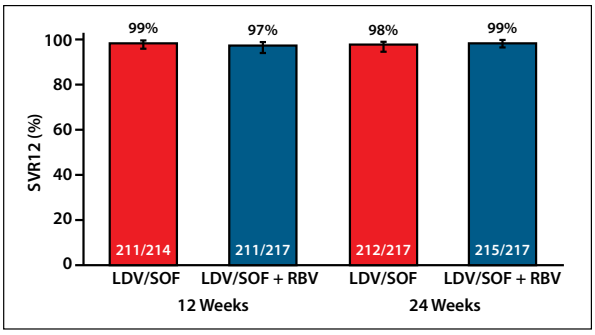


Figure 2. SVR12 rates in the ION-1 trial of sofosbuvir (SOF) plus ledipasvir (LDV), with or without ribavirin (RBV). ION-1, A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5885 Fixed-Dose Combination [FDC] +/- Ribavirin for 12 and 24 Weeks in Treatment-Naive Subjects With Chronic Genotype 1 HCV Infection; SVR12, sustained virologic response at week 12. Adapted from Mangia A et al. EASL abstract O164. *J Hepatol.* 2014;60(suppl 1).

The ION-1 Study of Sofosbuvir/Ledipasvir With or Without Ribavirin in Treatment-Naive Patients With Hepatitis C Genotype 1

The phase 3 ION-1 (A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5885 Fixed-Dose Combination [FDC] +/- Ribavirin for 12 and 24 Weeks in Treatment-Naive Subjects With Chronic Genotype 1 HCV Infection) trial evaluated regimens containing a once-daily, fixed-dose combination pill consisting of 2 direct-acting antiviral agents: the NS5B nucleotide polymerase inhibitor sofosbuvir (400 mg) and the NS5A inhibitor ledipasvir (90 mg). Sofosbuvir is approved as a once-daily, oral 400-mg tablet for use in combination with other agents for treating chronic HCV infection. Ledipasvir, an investigational drug, has shown picomolar potency against HCV genotypes 1a and 1b. The trial compared 12 weeks vs 24 weeks of the sofosbuvir/ledipasvir fixed-dose combination pill with or without ribavirin. Results were presented by Dr Alessandra Mangia of the Ospedale Casa Sollievo della Sofferenza in San Giovanni Rotondo, Italy at the EASL 2014 meeting (Abstract O164).

The 865 enrolled patients had HCV genotype 1 and were treatment-naive. The primary endpoint was sustained virologic response or undetectable viral load, assessed 12 weeks after discontinuation of the study drug. Approximately 60% of patients were male, and the mean age was 52 years. Patients were randomized across 4 treatment arms to receive the sofosbuvir/ledipasvir combination pill with or without ribavirin for 12 weeks or 24 weeks.

Nearly all patients in the 4 treatment arms achieved a cure. Among patients receiving ribavirin, SVR rates at 12 weeks and 24 weeks were similar (97% vs 99%, respectively). Treatment without ribavirin yielded similar results at 12 and 24 weeks (99% vs 98%, respectively; Figure 2). Among the 431 patients who received 12 weeks of treatment with or without ribavirin, 11 patients (2.5%) did not achieve an SVR12. However, only 1 of these patients relapsed. (The remaining 10 patients were lost to follow-up.) Patients with HCV subtypes 1a and 1b had similar cure rates. The presence of cirrhosis did not affect rates of SVR12.

Treatment-emergent severe AEs were reported in 32 patients (4%) receiving sofosbuvir plus ledipasvir. The most frequent AEs reported with this therapy were headache (25%), fatigue (23%), and nausea (12%). Among patients not receiving ribavirin, none in the 12-week group and 2 in the 24-week group discontinued treatment because of AEs.

Presentations in IBS

Linaclotide Reduces Bloating in Patients With Chronic Idiopathic Constipation

Bloating is a common symptom of chronic idiopathic constipation, and effective treatments are lacking. Linaclotide is a minimally absorbed, peptide agonist of guanylate cyclase-C (GC-C) approved in the United States for the treatment of chronic idiopathic constipation. At Digestive Disease Week 2014, Dr Brian Lacy of the Geisel School of Medicine at Dartmouth University in Lebanon, New Hampshire presented findings from a double-blind, phase 3b clinical trial of linaclotide in chronic idiopathic constipation patients with bloating (Abstract Sa2008). Chronic idiopathic constipation patients with prominent bloating at baseline were randomized to oral linaclotide (145 µg or 290 µg once daily) or placebo. Eligible patients had a mean baseline bloating score of at least 5, based on a 0 to 10 numerical rating scale in which 0 represents no bloating and 10 represents very severe bloating. Patients reported on bowel symptoms, including spontaneous bowel movements, complete spontaneous bowel movements, stool consistency, and straining, as well as abdominal symptoms, including bloating, discomfort, pain, cramping, and fullness. The intent-to-treat population included 483 patients.

Linaclotide was associated with significant improvements over placebo in the primary endpoint; for at least 9 of 12 treatment weeks, the weekly complete spontaneous bowel movement rate was 3 or greater and increased by at least 1 complete spontaneous bowel movement from baseline in 16.4% of patients receiving linaclotide at 290 µg and 15.7% of patients receiving linaclotide at 145 µg vs 7.6% of placebo patients (P<.05).

Compared with patients in the placebo group, patients in both linaclotide dosage groups showed significant improvements after 12 weeks in endpoints representing abdominal bloating and in the change from baseline in the number of spontaneous bowel movements and complete spontaneous bowel movements per week (P<.05 for all endpoints). Both linaclotide groups also demonstrated improvement in the proportion of patients with spontaneous bowel movements occurring at least 24 hours after the first dose of study drug (P<.05 vs placebo). Both linaclotide doses yielded similar outcomes, significantly improving bloating within 1 week compared with placebo and providing a sustained benefit over the 12 weeks of study treatment. Diarrhea was the most common AE and was reported in 5.9% and 16.9% of patients receiving linaclotide 145 µg or 290 µg, respectively, and in 2.3% of patients receiving placebo.

Eluxadoline Improves IBS Symptoms in 2 Phase 3 Trials

Eluxadoline is a locally active, mixed µ opioid receptor agonist and δ opioid receptor antagonist in development for treating the abdominal pain and diarrhea associated with diarrhea-predominant irritable bowel syndrome (IBS-D). At Digestive Disease Week 2014, Dr Anthony Lembo of Beth Israel Deaconess Medical Center in Boston, Massachusetts presented results from 2 randomized, double-blind, placebo-controlled, phase 3 clinical trials that evaluated the efficacy and safety of eluxadoline in patients with IBS-D (Abstract 929d). Patients who met the Rome III criteria for IBS-D were randomized to treatment with eluxadoline (75 mg or 100 mg) twice daily or placebo, with efficacy evaluated through 26 weeks of treatment. Both trials had a primary endpoint of proportion of composite responders, defined as patients who reported an improvement in daily worst abdominal pain of at least 30% vs baseline and a daily stool consistency of less than 5 on the Bristol Stool Form Scale or absence of a bowel movement for at least 50% of days. Endpoints were evaluated through week 12 for the US Food and Drug Administration (FDA) responder endpoint and through week 26 for the European Medicines Agency (EMA) responder endpoint.

The 2 trials enrolled a total of 2428 patients; 66% were female. The patients' mean age was 45 years. Patients who received 100 mg of eluxadoline were significantly more likely to demonstrate FDA and EMA composite responses (P<.005). Similar responses were observed for patients who received 75 mg of eluxadoline, although the EMA response did not reach significance in 1 of the trials. Patients receiving the study drug were also more likely to have adequate relief of IBS symptoms compared with patients who received placebo. Both eluxadoline drug dosage groups showed significantly higher responder rates for the stool consistency component of the FDA and EMA responder endpoints compared with placebo, and both drug dosages yielded numerically higher responder rates for the pain component. Both eluxadoline dosage levels also showed greater improvements in the number of daily bowel movements and urgent episodes, daily IBS-D global symptom scores, and IBS quality-of-life scores (P<.05). The most com-

monly reported AEs were constipation (7.4% with 75 mg of eluxadoline, 8.3% with 100 mg of eluxadoline, and 2.4% with placebo) and nausea (7.8%, 7.3%, and 4.8%, respectively). Results were durable throughout the 26-week treatment period.

A New Biomarker Algorithm Helps Distinguish IBD From IBS

Although the Rome criteria define IBS based on characteristic symptoms, physicians typically perform diagnostic tests to exclude conditions such as inflammatory bowel disease (IBD) and colon cancer. At Digestive Disease Week 2014, Dr Stacy B. Menees of the University of Michigan Health System in Ann Arbor, Michigan presented results from a systematic review and meta-analysis investigating IBS biomarkers (Abstract Sa1079). The study evaluated the utility of commercially available tests of common serum and fecal biomarkers to distinguish between patients with IBS or IBD and healthy controls. The biomarkers were fecal calprotectin, fecal lactoferrin, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).

The analysis encompassed a systematic search of Medline, EMBASE, PubMed, Cumulative Index to Nursing and Allied Health Literature, and Web of Science and included prospective diagnostic cohort studies with any of the 4 biomarker tests in adults. Data were independently extracted by 3 authors. Parameters included IBS and IBD criteria, demographics, and levels of fecal calprotectin, fecal lactoferrin, CRP, and ESR. The study calculated the estimated probabilities that a study subject was healthy or had IBS or IBD, based on specific values for the biomarkers, by using Bayes' Theorem to combine the results of the means and standard deviations of the biomarker logarithms as well as the prevalence of IBS and IBD.

The analysis included 12 articles describing tests for fecal calprotectin, 10 for fecal lactoferrin, 8 for CRP, and 12 for ESR. None of the tests were able to definitively distinguish between healthy volunteers and IBS patients. ESR as a single marker showed little utility in predicting the likelihood that a patient had IBS or IBD. Too few studies were available to draw meaningful conclusions regarding fecal lactoferrin. The CRP and fecal calprotectin levels provided valuable data; in a patient with a CRP level below 0.5 mg/dL or a fecal calprotectin level below 40 µg/g, the likelihood of IBD was less than 1%.

The combination of these 4 biomarkers at varying levels could exclude IBD at a probability of less than 0.01. This Bayesian analysis of fecal and serum biomarkers could provide a diagnostic tool to help physicians exclude IBD when diagnosing IBS.

Patients With IBS Display Altered Colonic Bacterial Fermentation

The pathophysiology of IBS has not been fully elucidated. However, the disorder is considered multifactorial, and dysbiosis of the gut microbiota leading to abnormal intestinal fermentation presents a plausible etiologic mechanism. At Digestive Disease Week 2014, Dr Chang Hwan Choi of the Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, South Korea presented findings from a study of intestinal fermentation in IBS patients (Abstract 28). The study included 38 patients whose symptoms met the Rome III criteria for IBS and 46 healthy controls. To better understand the altered intestinal intraluminal bacterial fermentation in patients with IBS, 2 surrogate markers—intestinal intraluminal pH and fecal short-chain fatty acids (SCFAs)—were evaluated. Intestinal intraluminal pH was measured using the wireless motility capsule. SCFAs, including acetate, propionate, butyrate, and lactate, were measured using capillary gas chromatography.

Mean total colonic pH levels were significantly lower in IBS patients compared with healthy controls (6.71 vs 7.37; P=.007). No differences were observed in total or segmental pH levels in the small bowel for IBS patients vs healthy controls. Consistent differences in intraluminal colonic pH were observed among all IBS subtypes. Lactate levels were significantly higher in IBS patients compared with healthy controls (4.44 vs 2.55 mmol/L; P=.035). No other significant differences were observed between the 2 patient groups for other SCFAs or for total SCFAs. A positive correlation was observed between IBS symptom severity scores and colonic pH levels (P=.01) and abdominal pain (P=.061). In contrast, no correlation was detected between IBS symptom severity or abdominal pain scores and small bowel pH or fecal SCFAs. The results of the study suggest that altered colonic bacterial fermentation plays an important etiologic role in the pathogenesis of IBS.

Guanylate Cyclase-C/cGMP Pathway Alterations Vary Among IBS Subtypes

In patients with IBS with constipation (IBS-C), linaclotide reduces abdominal pain and improves constipation. Mechanistically, linaclotide activates GC-C expressed on intestinal epithelial cells. The ensuing production and release of cGMP accelerates gastrointestinal transit and inhibits colonic nociceptors. Although key components of the GC-C/cGMP pathway are expressed on human colonic mucosa, the expression status of these components has not been elucidated in different IBS subtypes. Dr Andrea M. Harrington of the University of Adelaide

School of Medicine in Adelaide, Australia presented results of a study investigating this issue at Digestive Disease Week 2014 (Abstract Su2066).

Rectosigmoidal mucosal biopsies were obtained from IBS patients who met the Rome III criteria (n=14) and from healthy controls (n=10). Results were compared for patients with mixed bowel symptoms that included constipation and diarrhea (IBS-M; n=7) and for patients with IBS-C (n=7). Real-time polymerase chain reaction was used to assess mRNA expression of various components of the GC-C/cGMP pathway in biopsies, including GC-C (GUCY2C); the endogenous GC-C agonists guanylin (GUCA2A) and uroguanylin (GUCA2B); and the cGMP transporters MRP4 (ABCC4) and MRP5 (ABCC5). Expression of target genes was quantified relative to the housekeeping genes for 18S ribosomal RNA and GAPDH. Immunohistochemistry was used to determine the localization of the pathway signaling components relative to cellular structures in separate biopsies. In mucosal biopsies from healthy controls, the most abundantly expressed component of the GC-C/cGMP signaling pathway was guanylin, followed by (in order of decreasing expression levels) uroguanylin ($P<.01$), GC-C ($P<.001$), MRP5 ($P<.001$), and MRP4 ($P<.001$). Guanylin and uroguanylin expression was significantly reduced in IBS-M biopsies compared with those of healthy controls ($P<.05$). In contrast, IBS-C patient biopsies showed significantly decreased expression of MRP4 compared with those of healthy controls ($P<.001$). No significant difference in either MRP5 or GC-C expression emerged between IBS patient subtypes and healthy controls. Based on immunohistochemistry, MRP4 was expressed on the apical side of colonic epithelial cells, and MRP5 was expressed basolaterally. The study demonstrated distinct alterations in the expression of components of the GC-C/cGMP pathway among different IBS subtypes and may shed light on the pathophysiology of IBS.

Diet Affects Symptoms in IBS Patients

A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) has shown a potential benefit in the treatment of IBS. In nonceliac patients with IBS-like symptoms, a gluten-free diet may alleviate symptoms, consistent with nonceliac gluten sensitivity, which occasionally overlaps with IBS. Dr Daria Piacentino of the Department of Neurology and Psychiatry at Sapienza University in Rome, Italy presented results from a study on diet in IBS patients at Digestive Disease Week 2014 (Abstract 374). The study examined 3 diets that varied exposure to FODMAPs and/or gluten in patients with IBS to determine the effect on bloating, abdominal distension, and abdominal pain. The 3 diets included low FODMAP and gluten-free (FOD-GF), low FODMAP and normal gluten (FOD-NG), and normal FODMAP and normal gluten (control). The study recruited 60 consecutive outpatients who met Rome III criteria for IBS, including 37 women. Patients ranged in age from 21 years to 67 years. At enrollment, patients rated bloating severity with a visual analogue scale ranging from 0, indicating no or mild bloating, to 10, indicating very severe bloating. Patients completed a 2-week daily diary card to calculate the number of days with abdominal distension or pain. After the patients completed the diary, they were randomly assigned to 1 of the 3 dietary protocols for 4 weeks. During the last 2 weeks of the diet, patients completed a second diary card. At the end of the study, they again rated the severity of bloating.

All data were analyzed by an investigator blinded to the diet assignment. Baseline sociodemographic and clinical characteristics were well balanced among the 3 groups. After 4 weeks on the diets, the FOD-GF and FOD-NG groups showed significant improvements in bloating, abdominal distension, and pain ($P<.05$ for all comparisons). Patients in the control group experienced slight, nonsignificant improvement in the symptoms. One-way analysis of variance showed comparable severity of bloating and frequency of abdominal distension or pain, but a significant difference emerged for the same symptoms after 4 weeks of the study diet. The Tukey range test revealed improvement in IBS symptoms for patients on both diets compared with controls. There were no significant differences between the 2 test diets. In summary, eliminating gluten did not appear to provide an added benefit over the elimination of FODMAPs.

Presentations in IBD

A Study of Fecal Microbiota Therapy in Patients With Ulcerative Colitis

Although fecal microbiota therapy (FMT) can successfully treat *Clostridium difficile* colitis, its efficacy in treating active ulcerative colitis (UC) has yet to be clearly established. At Digestive Disease Week 2014, Dr Paul Moayyedi of the Department of Medicine at McMaster University in Hamilton, Ontario presented results of the first randomized, placebo-controlled trial investigating the efficacy of FMT in treating UC (Abstract 929c). Eligible patients were ambulatory, with active UC defined by a Mayo score of at least 4 and an endoscopic Mayo score of at least 1 with no upper limit. All enrolled patients tested negative for the *C difficile* toxin gene by polymerase chain reaction. Patients were allowed to continue taking any UC medications they had been consistently using during the previous weeks. No antibiotics were allowed within 30 days before enrollment. Examination with a flexible sigmoidoscopy was performed at baseline.

Patients were randomized to receive FMT given by a 50-mL retention enema from an anonymous donor, or placebo consisting of a 50-mL water enema, once per week for 6 weeks. The primary outcome was remission of UC, defined as a Mayo score of 2 or less with an endoscopic Mayo score of 0 at week 7. Secondary outcomes included health measures assessed by the Mayo score, the IBD questionnaire, and the EQ-5D.

At the time of the presentation, 53 patients had completed the study, and 10 patients were continuing on study treatment. Baseline characteristics were well balanced between the 2 treatment arms. Forty-five percent of patients had pancolitis and 42% were taking steroid medication, with 19% on immunomodulators and 9% on biologic therapy.

No differences were observed for the study treatment vs placebo in primary outcome or in any of the secondary outcomes. Although no patients were in remission at week 7, 16 patients in the FMT arm subjectively reported symptom improvement. After these patients continued on unblinded, weekly FMT for a further 6 to 12 weeks, 9 of 27 patients achieved remission (33%; 95% CI, 15%-51%). No major AEs were attributable to FMT. Dr Moayyedi and colleagues concluded that FMT could be effective over time periods longer than 6 weeks, but the therapy should be evaluated only in the context of clinical studies.

Persistent Antibodies to Infliximab Predict Loss of Response in IBD

IBD patients treated with infliximab may develop antibodies to infliximab (ATIs), which can reduce the efficacy of this therapy. In a poster presented at Digestive Disease Week 2014, Dr Manon Leclerc of Saint-Etienne University Hospital in Saint-Priest-en-Jarez, France provided results from a prospective study investigating the ability of ATIs to predict loss of response in patients with IBD (Abstract Sa1257). Loss of clinical response was defined as an increase in clinical symptoms requiring a therapeutic adjustment (eg, infliximab dose intensification, initiation of another medication, and surgery). CRP was followed as a marker of disease activity. The study included 481 blood samples from 93 consecutive IBD patients, including 59 with Crohn's disease, who were treated with infliximab. The patients' mean age was 30 years. The mean duration of follow-up was 17.2 months.

Loss of clinical response was demonstrated in 32 patients (34.4%). Thirty-four patients (38%) had normal levels of CRP, and 27 patients (29%) had detectable ATIs. Among the patients with ATIs, a slight majority (51.9%) had only 1 ATI-positive sample; in 48.1%, more than 50% of the samples were ATI-positive. The presence of ATIs was significantly associated with loss of response (P=.011) and positive CRP (P=.0003). ATIs exceeding 20 ng/mL in the first sample predicted loss of response with 94% specificity and 22% sensitivity (likelihood ratio, 3.39; area under the receiver operating characteristic curve, 0.59). An increasing number of consecutive samples positive for ATIs correlated to an increasing likelihood of loss of response. The presence of positive ATIs in more than 50% of a patient's samples was associated with more than 50% loss of response to infliximab during follow-up, and permanent ATIs were associated with systematic clinical relapse (P=.0044). However, transient ATIs (present in only 1 sample) were not associated with loss of response (P=.01; Figure 3). Other factors not associated with loss of response included concomitant thiopurines, and infliximab duration and dose. A univariate analysis showed that loss of response corresponded to an ATI level greater than 20 ng/mL (P=.0071), CRP levels greater than 5 mg/L (P=.0046), and clinical activity (P=.0026). A multivariate analysis was used to calculate the relative risks associated with maintaining clinical remission; they were 0.64 (95% CI, 0.46-0.90) for an ATI level greater than 20 ng/mL and 0.65 (95% CI, 0.43-0.90) for a CRP level greater than 5 mg/L. These 2 factors combined produced an increased relative risk of 0.21 (95% CI, 0.08-0.55).

C-Reactive Protein Predicts Histologic Activity in Patients With Ulcerative Colitis

Although mucosal healing has emerged as a new therapeutic goal for patients with UC, it may not accurately indicate histologic remission. Persistent microscopic inflammation is associated with an increased risk of colorectal neoplasia

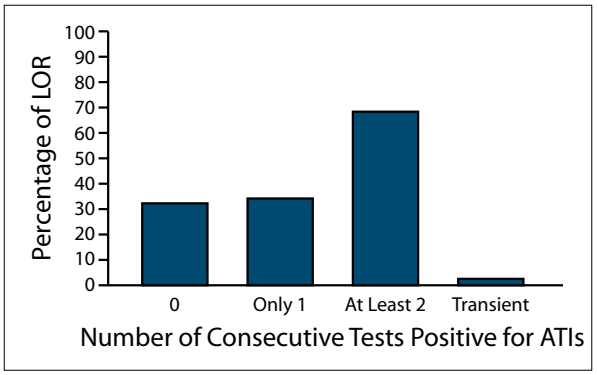


Figure 3. Correlation between LOR and consecutive positive measurement of ATIs. ATIs, antibodies to infliximab; LOR, loss of response. Adapted from Leclerc M et al. DDW abstract Sa1257. *Gastroenterology*. 2014;146(suppl 1).

and may predict an increased risk of colectomy and hospitalization. Therefore, histologic remission is gaining use as a clinical trial endpoint in studies of UC. At Digestive Disease Week 2014, Dr Britt Christensen of the University of Chicago Department of Medicine in Chicago, Illinois described results of a study that examined the prevalence and possible predictors of mucosal healing, histologic remission, and mucosal healing without histologic remission in patients with confirmed UC (Abstract 964). The study identified patients who had undergone a baseline colonoscopy with biopsies taken in each colon segment (rectum, left side, and right side) and a follow-up colonoscopy more than 1 year later. Each colonic segment of the final colonoscopy was retrospectively evaluated for mucosal healing, defined as normal mucosa or quiescent inflammation by endoscopy, and for histologic remission, defined by the absence of residual histologic inflammation. The primary outcomes were mucosal healing, histologic remission, and mucosal healing without histologic remission.

The study included 646 patients with a median age of 29 years (range, 5-82 years), of whom 60.0% had mucosal healing and 50.3% had histologic remission. Mucosal healing was strongly associated with histologic remission (OR, 13.41; 95% CI, 7.137-26.128; *P*<.001). Multivariate analysis revealed several predictors of mucosal healing, including longer duration of disease (*P*=.004), current therapy with an anti-TNF treatment (*P*=.019), current therapy with an antimetabolite (*P*=.037), and a CRP level of less than 3.0 mg/L (*P*=.002). Among the 385 patients who had mucosal healing, 80 (20.8%) had ongoing histologic activity. Multivariate analysis revealed that a CRP level above 2.9 mg/L was the only variable predictive factor of ongoing histologic activity in patients with mucosal healing (adjusted OR, 3.56; 95% CI, 1.55-8.16; *P*=.003). In summary, although the presence of mucosal healing was strongly associated with histologic remission, biopsy revealed histologic activity in approximately 21% of patients with mucosal healing, and a CRP level greater than 2.9 mg/L predicted ongoing histologic activity in patients with complete mucosal healing.

A Higher Dose of Mesalamine Reduces Fecal Calprotectin Levels in Ulcerative Colitis Patients

In patients with quiescent UC, lower concentrations of fecal calprotectin are associated with lower rates of relapse. At Digestive Disease Week 2014, Dr Mark T. Osterman of the Hospital of the University of Pennsylvania in Philadelphia, Pennsylvania presented results from a study examining mesalamine and fecal calprotectin levels (Abstract 862). The randomized controlled trial evaluated whether higher doses of mesalamine can reduce the concentration of fecal calprotectin in patients with quiescent UC. Enrolled patients had UC in remission (based on the Simple Clinical Colitis Activity Index), were taking no more than 3 g/day of mesalamine, and had a fecal calprotectin concentration exceeding 50 µg/g. As needed, the patients were switched to multimatrix mesalamine at 2.4 g/day for 6 weeks prior to randomization. Patients were evenly randomized to continue their current mesalamine dose or to increase the dose by 2.4 g/day for 6 weeks. The primary outcome was continued remission with fecal calprotectin concentration of less than 50 µg/g at 6 weeks. Secondary outcomes included continued remission with a fecal calprotectin concentration below 100 µg/g; this level was increased to less than 200 µg/g among patients who presented with 200 µg/g at baseline.

The study randomized 52 patients from 119 screened. The primary outcome was met by 7 of 26 patients (26.9%) randomized to dose escalation and by 1 of 26 control patients (3.8%; *P*=.0496). A greater proportion of patients in the dose-escalation group achieved a reduction in fecal calprotectin concentration to below 100 µg/g (52.6% vs 15.8%; *P*=.04)—or to below 200 µg/g for patients with fecal calprotectin concentrations above this level prior to randomization (76.9% vs 16.7%; *P*=.005)—than patients receiving placebo. At 6 weeks after randomization, the median change in fecal calprotectin concentration was -11 µg/g (interquartile range, -231 to 101) in the control group and -70 (interquartile range, -378 to 4) in the dose-escalation group (*P*=.28). After adjusting for baseline fecal calprotectin concentration, the dose-escalation group showed a trend toward a greater reduction at 6 weeks (*P*=.06). Among patients who were still in remission after the 6-week randomization phase, clinical relapse occurred more quickly among those with a fecal calprotectin concentration above 200 µg/g compared with patients showing a lower fecal calprotectin concentration (*P*=.01). Time to relapse was shorter for patients with a fecal calprotectin concentration below 100 µg/g (*P*=.09).

Table 1. Predictors of Recurrence: Univariate Analysis

	Endoscopic Recurrence			Clinical Recurrence
	Odds Ratio	**95% CI**	***P* Value**	***P* Value**
ASCA IgA >90 EU	0.93	0.32-2.67	.894	.969
ASCA IgG >94 EU	0.09	0.01-0.69	.004	.073
CBir1 >80 EU	1.23	0.44-3.42	.689	.968
Fla2 >66 EU	3.42	1.28-9.12	.011	.021
FlaX >92 EU	3.42	1.28-9.12	.011	.063
OmpC >13 EU	1.61	0.59-4.36	.351	.407
pANCA positivity	3.27	1.16-9.24	.021	.008
CRP >5 mg/L	2.64	0.99-7.06	.049	.761
Active smoking	2.90	1.11-7.60	.027	.019

ASCA, anti–*Saccharomyces cerevisiae* antibodies; CRP, C-reactive protein; Ig, immunoglobulin; OmpC, outer membrane porin C; pANCA, perinuclear antineutrophil cytoplasmic antibody. Data from Ferrante M et al. DDW abstract Su1349. *Gastroenterology*. 2014;146(suppl 1).

Preoperative Serologic Markers May Predict Postoperative Recurrence of Crohn's Disease

In a poster presented at Digestive Disease Week 2014, Dr Marc Ferrante of the Leuven University Hospitals in Leuven, Belgium described results from a study evaluating the use of preoperative serologic markers to predict postoperative clinical and endoscopic recurrence of Crohn's disease (Abstract Su1349). The study enrolled 100 consecutive patients; their median age was 41.7 years, and 41 were men. All patients were undergoing ileal resection with ileocolonic anastomosis for refractory Crohn's disease. A serum sample was collected from each patient within 1 week before surgery. All patients were followed prospectively with postoperative endoscopic evaluation at 6 months. The primary endpoint was endoscopic recurrence, and the secondary endpoint was time to clinical relapse. Blinded sera were analyzed by the enzyme-linked immunosorbent assay at an independent laboratory for the expression of the anti–*Saccharomyces cerevisiae* antibodies immunoglobulin A and immunoglobulin G and the atypical antibody perinuclear antineutrophil cytoplasmic antibody (pANCA), and for antibodies against 3 flagellar markers (Fla2, FlaX, and CBir1) and the outer membrane porin C. Thirty-four patients had undergone prior resection, 26 had familial IBD, and 27 were active smokers. Baseline CRP was greater than 5 mg/L in 55 patients.

Endoscopic recurrence was observed in 25 patients, and clinical relapse within 24 months of follow-up was observed in 29 patients. Based on multivariate analysis, factors independently associated with endoscopic recurrence included an anti-Fla2 antibody level greater than 66 ELISA units (EU; OR, 3.0 [95% CI, 1.1-8.7]; *P*=.037) and active smoking (OR, 3.1 [95% CI, 1.1-8.8]; *P*=.029). Several factors were independently associated with clinical recurrence: an anti-Fla2 antibody level greater than 66 EU (OR, 2.2 [95% CI, 1.0-4.6]; *P*=.041), pANCA positivity (OR, 2.5 [95% CI, 1.2-5.4]; *P*=.016), and active smoking (OR, 2.6 [95% CI, 1.2-5.5]; *P*=.011; Table 1). A cumulative risk score was developed by combining the 3 risk factors associated with endoscopic or clinical recurrence. It successfully predicted the likelihood of both endoscopic relapse (*P*<.001) and clinical relapse (*P*<.001), and showed that an increasing number of risk factors corresponded to a gradual increase in the relapse rate.

Reduced Serum and Fecal Infliximab Levels in Nonresponding Ulcerative Colitis Patients

Some patients with UC exhibit a primary nonresponse to infliximab, an antibody that binds to TNF-α. The mechanism that causes this reaction is not fully understood. One possible cause may be a high inflammatory load, which presents a large concentration of TNF-α for neutralization and therefore reduces the efficacy of the antibody, leading to insufficient serum antibody concentrations. At Digestive Disease Week 2014, Dr Johannan F. Brandse of the Academic Medical Center in Amsterdam, the Netherlands presented results of a pharmacokinetic study addressing the relationship between infliximab serum and fecal concentrations and efficacy (Abstract 786). This multicenter, prospective, observational study enrolled patients with moderate-to-severe UC. Patients had no prior exposure to anti–TNF-α therapy. After baseline endoscopy, patients began infliximab treatment. Serum infliximab concentrations, ATIs, and fecal samples were collected at 10 serial time points during the first 6 weeks of induction therapy. Response was defined as endoscopic improvement at weeks 6 to 8. Pharmacokinetic analysis was performed by nonlinear mixed-effects modeling and described using a 2-compartment pharmacokinetic model.

Among the 15 enrolled patients, 7 (46.7%) were receiving treatment with concomitant thiopurines. Eight patients

(53.3%) showed no endoscopic improvement. Median trough levels before the third infliximab infusion during week 6 were 2.5 µg/mL for endoscopic nonresponders and 8.2 µg/mL for responders (*P*=.03). Serum infliximab levels of 7 µg/mL or less at day 42, defined as a cutoff point, predicted endoscopic nonresponse, with an OR of 36 (*P*=.03). At week 6, 4 patients developed ATIs; their antibody clearance increased by 4.4-fold and their peripheral volume of distribution decreased by 5%. Nonresponders showed a significantly higher concentration of fecal infliximab on day 1 (*P*=.02). Average post hoc area under the infliximab concentration vs the time curve was 1204±507 mg/L/day in nonresponders vs 1417±444 mg/L/day for responders (*P*=.42).

AJM300 Shows Efficacy in Ulcerative Colitis

Selective inhibition of lymphocyte trafficking is a promising treatment for patients with UC; however, virtually all drug candidates are monoclonal antibodies. AJM300 is an orally available small-molecule antagonist of the α4 integrin. In cells that express the α4β1/α4β7 integrin, AJM300 inhibits cellular binding to VCAM-1/MAdCAM-1. At Digestive Disease Week 2014, Dr Mamoru Watanabe of the Department of Gastroenterology and Hepatology at Tokyo Medical and Dental University in Tokyo, Japan presented findings from a randomized, placebo-controlled, phase 2a study of the α4 integrin inhibitor in UC patients (Abstract 370). The study enrolled 102 Japanese patients with moderately active UC as evidenced by a Mayo Clinic score of 6 to 10, an endoscopic subscore of 2 or less, and a rectal bleeding score of 1 or less. Patients were required to have documentation of inadequate response or intolerance to mesalamine or corticosteroids. They were randomized to receive AJM300 (960 mg) or placebo 3 times daily for 8 weeks. The primary endpoint was a clinical response at week 8, defined as a reduction in the Mayo Clinic score by 3 or more points and a decrease of at least 30% from baseline, with a concomitant decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1. Key secondary endpoints included clinical remission and mucosal healing at week 8.

The study met its primary endpoint by showing that a greater proportion of patients in the AJM300 treatment arm achieved a clinical response at week 8 compared with placebo (62.7% vs 25.5%; OR, 5.25; 95% CI, 2.23-12.82; *P*=.0002). Secondary endpoints were also met, as demonstrated by clinical remission rates at week 8 of 25.3% with AJM300 vs 3.9% with placebo (OR, 7.81; 95% CI, 1.64-37.24; *P*=.0099) and mucosal healing at week 8 of 58.8% with AJM300 vs 29.4% with placebo (OR, 4.65; 95% CI, 1.81-11.90; *P*=.0014). Significant increases in peripheral lymphocyte counts at weeks 2 and 4 were observed in the AJM300 arm only, without any change in neutrophil counts. AJM300 was well tolerated, with no serious AEs or serious infections observed. This study is the first to demonstrate the clinical benefit of an oral α4 integrin antagonist for patients with IBD.

Third Trimester Exposure to Biologic Therapy Does Not Increase Infant Infection Rates

The administration of infliximab or adalimumab in pregnant women is of interest because active placental transfer of the antibodies may occur, with the drugs persisting in the newborn for up to 6 months. Certolizumab pegol is another therapeutic anti–TNF-α antibody, but it has passive placental transfer, resulting in low infant serum drug concentrations. Use of anti–TNF-α antibodies during the third trimester of pregnancy is controversial, given concerns of increased infant infections and possible alterations to the developing immune system. At Digestive Disease Week 2014, Dr Uma Mahadevan of the University of California San Francisco School of Medicine in San Francisco, California presented results from a study showing that women with IBD can safely continue anti–TNF-α therapeutic antibody monotherapy throughout pregnancy (Abstract 960).

The analysis included a prospective cohort of pregnant women who were part of the PIANO (A 1000 Patient Prospective Registry of Pregnancy Outcomes) registry at 30 US IBD centers. Patients were followed through pregnancy and the first 4 years of the child's life. This study analyzed use of biologics at 2 different time points: in the third trimester and in the first and second trimesters together. Women who received biologic therapy in their third trimester were compared with those who had not received it during this time, and women who received biologic therapy in their first and second trimesters, but not the third, were compared with those who had not received it during the first and second trimesters. Among the 1289 women enrolled, 1097 had completed their pregnancy, resulting in 1039 live births. Biologics were used by 501 women during pregnancy. Exposure in trimester 3 was reported in 422 women; they were compared to 597 women who had not been exposed in the third trimester. Seventy patients had received biologics in trimester 1 or 2.

No increased risk was observed for women exposed to biologics vs those who were not exposed, based on preterm birth (OR, 1.3), disease activity in term 3 (OR, 0.8), postpartum disease activity (OR, 1.2), and risk of infection at month 4, 9, or 12 (ORs, 0.9, 1.1, and 1.1, respectively). However, infants who were exposed in utero to an anti–TNF-α antibody plus azathioprine/6-mercaptopurine showed higher rates of preterm birth, after adjusting for IBD activity (OR, 2.6; *P*<.05). In-utero exposure to combination therapy also increased the rates of preterm birth (OR, 4.9), low birth weight (OR, 6.1), and admission to neonatal intensive care (OR, 3.9) in mothers with UC.

Presentations in GERD

Evidence of a Significant Association Between GERD and Myocardial Infarction

Gastroesophageal reflux disease (GERD) affects approximately 40% of the adult population in the United States. It is known that immune cells promote the formation of atherosclerotic lesions in the coronary arteries, and numerous proinflammatory molecules are commonly elevated in patients with GERD. At Digestive Disease Week 2014, Dr Ravi K. Prakash of the MetroHealth System in Cleveland, Ohio presented results of a study investigating whether the incidence of myocardial infarction (MI) is higher in patients with GERD (Abstract 722). The case-control study collected data from the Explorys database, a private, cloud-based health data aggregator that contains health data for more than 35 million patients in the United States. The study identified an aggregated cohort of eligible GERD patients who underwent an esophagogastroduodenoscopy (EGD). A control group consisted of all patients ages 18 to 85 years without GERD who had never undergone EGD. Patients with known prior coronary or peripheral arterial disease were excluded.

There were 316,390 patients in the GERD arm and 13.6 million in the control arm. Throughout the next 5 years, a first MI occurred in 5.96% of the GERD arm (18,860 cases) vs 1.05% in the control arm (144,140 cases). Therefore, in patients without known coronary or peripheral arterial disease at baseline, GERD was associated with a 57% increased risk of having a first acute MI within the next 5 years. The incidence of new MI was higher in GERD patients who were male, obese, or had hypertension ($P<.05$ for all). Multivariate logistic regression analysis that adjusted for 6 major cardiovascular risk factors showed a 49% increase in relative risk (RR) of MI associated with obesity, a 90% increase associated with smoking, and a 10% increase associated with hypertension. The incidence of a new MI was highest in obese male patients with GERD and hypertension compared with the control patients ($P<.0001$).

Transoral Incisionless Fundoplication Reduces GERD Symptoms

Proton pump inhibitor (PPI) therapy can prevent GERD symptoms, allow healing of the esophagus, and prevent the return of esophagitis. However, a known limitation of these drugs is the incomplete control of regurgitation and extraesophageal symptoms. Transoral incisionless

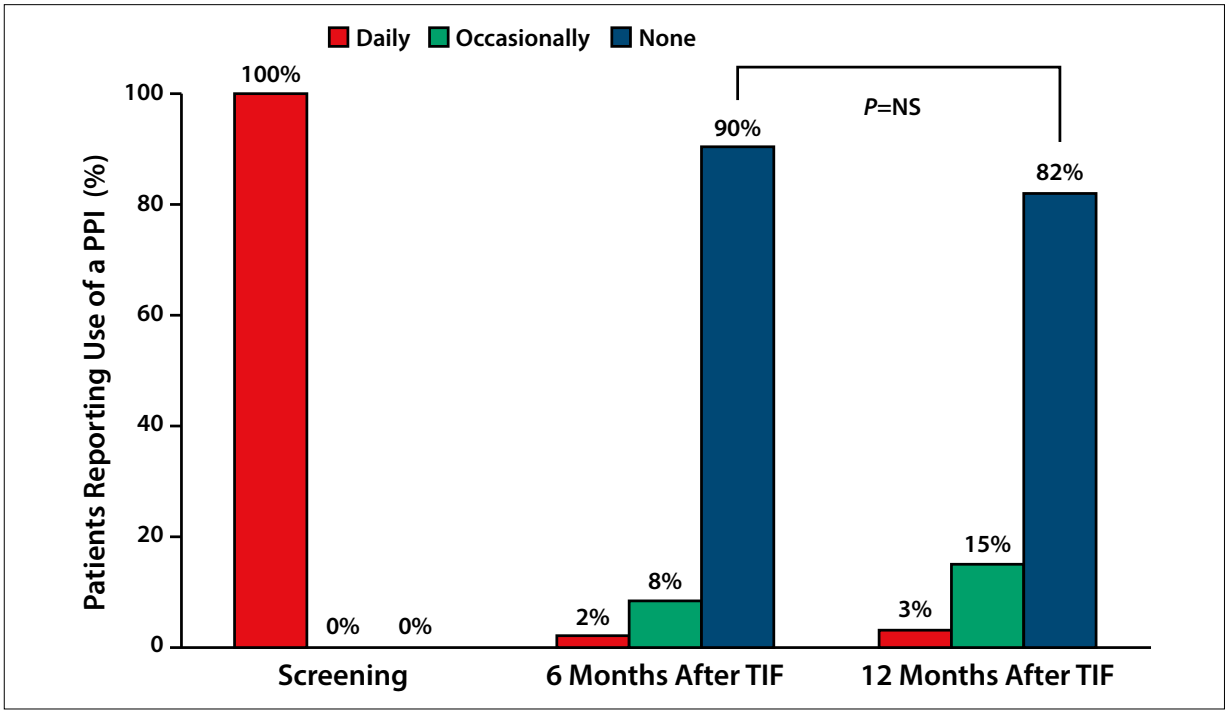


Figure 4. PPI use after the TIF procedure in the TEMPO trial. NS, not significant; PPI, proton pump inhibitor; TEMPO, Transoral Incisionless Fundoplication EsophyX vs Medical PPI Open Label Trial; TIF, transoral incisionless fundoplication. Adapted from Trad KS et al. DDW abstract 724. *Gastroenterology.* 2014;146(suppl 1).

fundoplication (TIF) surgery is a variant of traditional fundoplication that is conducted transorally rather than laparoscopically and may serve as an alternative to the use of PPIs. At Digestive Disease Week 2014, Dr Karim S. Trad of the George Washington University School of Medicine and Health Sciences in Washington, DC presented results of a study comparing PPIs to surgery (Abstract 724). The TEMPO (Transoral Incisionless Fundoplication EsophyX vs Medical PPI Open Label) trial randomized 63 patients with small hiatal hernias at 7 community hospitals in the United States. Patients in the PPI group received the maximum standard dose. Patients in the surgery group underwent esophagogastric fundoplication. The primary outcome was elimination of daily regurgitation or extraesophageal symptoms, which were evaluated with the GERD HRQL Scale, the Reflux Symptom Index, and the Reflux Disease Questionnaire. Secondary outcomes included normalization of distal esophageal acid exposure, PPI usage, and healing of esophagitis.

The analysis included 39 TIF patients and 21 PPI patients. All patients had objective evidence of GERD with abnormal esophageal acid exposure. They had experienced symptoms for a median of 10 years, and they had been receiving PPIs for a median of 8 years.

Use of PPIs was dramatically reduced after the TIF procedure (Figure 4). After 6 months of follow-up, regurgitation was eliminated in 97% of TIF patients vs 50% of PPI patients (RR, 1.9; 95% CI, 1.2-3.1; *P*=.006). Elimination of regurgitation and extraesophageal symptoms occurred in 62% of TIF patients and 5% of PPI patients (RR, 12.9; 95% CI, 1.9-88.9; *P*=.009). Although only 5% of patients in the PPI arm reported elimination of regurgitation and extraesophageal symptoms after the initial 6-month period, this proportion increased to 67% (14 of 21 patients) 6 months after these patients crossed over and underwent TIF (*P*<.001). In addition, 71% of the crossover patients were completely off PPIs 6 months after undergoing TIF. Esophageal acid exposure was normalized in 54% of TIF patients vs 52% of PPI patients (RR, 1.0; 95% CI, 0.6-1.7; *P*=.914). Heartburn was eliminated in 90% of TIF patients vs 13% of PPI patients (*P*<.001).

An Endoscopic Stapling Device Reduces PPI Use in GERD Patients

Although PPIs provide adequate control of GERD for many patients, surgery is often necessary for patients with refractory disease and is an option for patients wishing to avoid the AEs and costs associated with long-term PPI therapy. An endoscopic stapling device employs a flexible surgical stapler plus an endoscopic video camera and an endoscopic range finder that can be used to create an anterior fundoplication. At Digestive Disease Week 2014, Dr William R. Kessler of the Witham Memorial Hospital in Lebanon, Indiana presented 3-year results from a prospective trial of patients treated with the stapling device (Abstract Tu1396). Patients had GERD documented by a pH probe and had responded well to PPI therapy. Patients were placed under general anesthesia and received 2 to 3 staple quintuplets to create anterior fundoplication. Phone interviews were used to collect follow-up data, which included a minimum of 3 years' postprocedure GERD-HRQL scores, patients' overall satisfaction, and information on use of PPIs, histamine-2 receptor antagonists, and antacids.

Twenty-two patients underwent surgical stapling at a single institution. One patient experienced a gastrointestinal bleed 8 days after the procedure and required a blood transfusion, after which bleeding stopped spontaneously. Mean GERD-HRQL scores improved at 1, 2, and 3 years. For the 14 patients who were off daily PPIs, the mean GERD-HRQL score improved from 30.6 at baseline to 6.8 at year 3. For the 5 patients who were still receiving daily PPIs, the improvement was from 12.2 to 8.8. The proportions of patients who reported satisfaction with the procedure were 67% at 1 year, 78% at 2 years, and 63% at 3 years. Most patients remained off daily PPIs at all time points. Among the patients who continued on a PPI after the stapling procedure, mean omeprazole equivalent doses were decreased from a baseline level of 47.7 mg/day to 26.8 mg/day at 1 year, 19.7 mg/day at 2 years, and 15.9 mg/day at 3 years. Fewer than 5% of patients experienced complications, and 74% of patients remained off daily PPIs at 3 years after the procedure.

The Effect of Proton Pump Inhibitors on the Risk of Esophageal Adenocarcinoma in Patients With Barrett Esophagus

Patients with Barrett esophagus are at increased risk for esophageal adenocarcinoma (EAC). Studies presented at Digestive Disease Week 2014 offered conflicting findings regarding whether the use of PPIs decreases the risk of EAC.

Dr Srinivas Gaddam of the Washington University School of Medicine in Saint Louis, Missouri presented results from a prospective study evaluating the association between the use of PPIs and statins with the development of high-grade dysplasia and EAC (Abstract 710). The study, conducted by the Barrett's Consortium Group, investigated a large cohort of Barrett esophagus patients undergoing screening and/or surveillance at 5 centers. The diagnosis of Barrett esophagus included intestinal metaplasia in the columnar epithelium in the distal esophagus. The primary endpoint of progression to high-grade dysplasia or EAC included both prevalent and incident cases, based on the assumption that clinical and demographic factors of patients in both categories should be similar.

The study analyzed 3635 patients, with a mean age of 60.9 years. Most patients (87.8%) were male. Patients had a mean body mass index of 28.4 kg/m^2 (standard deviation, 6.1 kg/m^2) and a mean Barrett esophagus length of 3.5 cm (standard deviation, 3.3 cm). The study population included 506 cases with high-grade dysplasia/EAC. Univariate analysis using Chi-square and Mann-Whitney U tests revealed several significant risk factors for high-grade dysplasia/EAC: age, male sex, longer Barrett esophagus length, smoking (currently or previously), hiatal hernia, and presence of visible lesions within the Barrett esophagus segment. Protective factors included use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs), PPIs, and statins (all P<.05). PPI use emerged as a significant protective factor (OR, 0.41; 95% CI, 0.22-0.75; P=.004) based on a statistically significant logistic regression model that adjusted for male sex, white race, Barrett esophagus length, use of H2 receptor antagonists, past or present smoking history, and aspirin or NSAID use. However, statin use did not provide an independent protective effect (OR, 0.73; 95% CI, 0.5-1.7; P=.10). Consistent with a protective effect conferred by PPI use, patients who did not develop high-grade dysplasia/EAC had a longer duration of PPI use compared with patients who developed high-grade dysplasia/EAC (4.2 years vs 3.2 years; P=.02).

Contrasting data were presented by Dr Gwen Masclee of the Maastricht University Medical Center in Maastricht, the Netherlands. Dr Masclee described a case-control study evaluating the influence of NSAIDs, statins, and PPIs on the risk of EAC in Barrett esophagus patients (Abstract Sa1837). The study cohort consisted of Barrett esophagus patients from 2 primary care databases, one in the United Kingdom and the other in the Netherlands, who were treated from 1996 through 2013. Adult patients with a diagnosis of EAC at least 1 year after the Barrett esophagus diagnosis were compared with an age-matched control group of patients without EAC. Year of Barrett esophagus diagnosis, body mass index, smoking history, and alcohol use were examined as confounding factors.

The study identified 15,134 patients, including 45 with EAC and 12 with high-grade dysplasia. Risk of EAC did not correlate to the presence of hiatal hernia or the presence of esophagitis or gastritis upon diagnosis of Barrett esophagus. Risk of EAC was increased by current smoking (OR, 2.63; 95% CI, 1.1-6.1) and current excessive alcohol use (OR, 1.9; 95% CI, 1.0-3.7). Statin use spanning 2 to 3 years yielded an OR of 0.66 (95% CI, 0.08-5.23) and an adjusted OR of 0.65 (95% CI, 0.08-5.11). For statin use of at least 3 years, the OR was 0.51 (95% CI, 0.14-1.86), and the adjusted OR was 0.48 (95% CI, 0.13-1.74). Increasing cumulative doses of statins yielded an OR of 0.58 (95% CI, 0.19-1.79) and an adjusted OR of 0.52 (95% CI, 0.17-1.63). Inclusion of the high-grade dysplasia endpoint yielded an OR for NSAID use of 0.98 (95% CI, 0.50-1.94) and an adjusted OR of 0.95 (95% CI, 0.48-1.89). For statin use of 2 to 3 years or greater than 3 years, ORs were 0.69 (95% CI, 0.09-5.43) and 0.54 (95% CI, 0.15-1.96), respectively, and adjusted ORs were 0.68 (95% CI, 0.09-5.36) and 0.54 (95% CI, 0.15-1.97), respectively. NSAID use was associated with a nonsignificant risk reduction of 2%. PPI use did not influence risk of EAC or the combined outcome of EAC and high-grade dysplasia.

A Novel Medical Device Reduces Symptoms of Extraesophageal Reflux

Extraesophageal reflux (EER) is caused by reflux of gastroduodenal contents into the laryngopharynx and results in symptoms such as chronic cough (CC), hoarseness, and globus pharyngeus. Although PPIs are often not effective in the treatment of EER, they are frequently prescribed. A novel medical device was developed to address the need for effective treatment in these patients. At Digestive Disease Week 2014, Dr Michael F. Vaezi of the Vanderbilt University Medical Center in Nashville, Tennessee presented results from a prospective study investigating the efficacy and safety of the upper esophageal sphincter (UES) assist device for patients with suspected EER (Abstract 725). The multicenter study included patients with extraesophageal symptoms and a reflux symptom index (RSI) score of greater than 13. Predominant symptoms at presentation included CC, choking, aspiration, chronic postnasal drip, globus pharyngeus, sore throat, and throat clearing. Each patient was individually fitted with a UES assist device that was adjusted to apply pressure above 20 mmHg to the external cricoid area, and external monitors ensured that this level was maintained throughout the study. The study's primary efficacy endpoint was reduction in RSI score at 4 weeks from baseline, with safety analysis based on AEs.

Forty-seven patients completed the study protocol at 4 centers. Patients had a mean age of 50 years and a median body mass index of 25.8 kg/m^2 (interquartile range, 23-29 kg/m^2). Most patients (72%) were female. The most common troublesome symptoms included CC (28%), excess mucus/postnasal drip (19%), throat clearing (11%), and hoarseness (11%).

The study met its primary efficacy outcome based on a reduction in the median RSI score from 27 (95% CI, 21-32) at baseline to 12 at week 4 (95% CI, 7-19). An improvement of greater than 25% was reported by 86% of patients, and 30% of patients reported an improvement of at least 75%. Mean improvement from baseline was 54%±28.1%, with 75% of patients and 92% of provid-

ers reporting satisfaction with the UES assist device. AEs were generally mild and included device technical issues in 14% of patients and mild skin irritation in 8%.

Pathologic Acid Exposure Time and Baseline Impedance Correlate With Probability of Response to Proton Pump Inhibitors

GERD may account for up to 90% of patients with CC. Patients with CC usually have normal results on multichannel intraluminal impedance–pH monitoring (MII-pH), and they often have an unsatisfactory response to PPIs. Measurement of the esophageal impedance baseline value in patients with typical symptoms appears to increase the sensitivity of MII-pH. At Digestive Disease Week 2014, Dr Mentore Ribolsi of the Campus Bio-Medico in Rome, Italy presented results from a prospective trial that evaluated characteristics of the reflux pattern and the role of MII-pH variables in predicting PPI response (Abstract Tu1850). Patients with CC persisting for at least 8 weeks and no evidence of esophagitis were selected from 3 hospitals in Italy. Patients without respiratory diseases underwent MII-pH and thus received a double dose of PPIs for 6 weeks or longer. The Fisman cough severity/frequency score was assessed before and after MII-pH. The control group included 60 patients with nonerosive esophageal reflux disease with typical symptoms. Pathologic impedance baseline value was defined as less than 1944.

Among the 156 CC patients, 68 (43.5%) had responded to PPIs. A pathologic acid exposure time was seen in 31 responders (46%) and 15 (17%) nonresponders. Patients with CC had a higher number of reflux episodes than patients with typical symptoms, regardless of whether they responded to treatment with PPIs (58.5 and 56.5, vs 41.0, respectively). Weakly acidic refluxes occurred in a larger proportion of nonresponder CC patients (53%) than in CC responder patients (37%) and patients with typical symptoms (36%). Among the nonresponders, 43 patients (49%) had pathologic acid exposure time or impedance baseline values; 15 patients (17%) presented with pathologic acid exposure time only ($P<.001$). The probability of a PPI response was increased 2-fold in CC patients with a pathologic acid exposure time, a pathologic impedance baseline value, or both compared with patients who exhibited a normal acid exposure time and impedance baseline value. Dr Ribolsi and colleagues concluded that an impedance baseline value is a promising variable that increases the diagnostic yield of MII-pH in patients with CC.

Presentations in Endoscopy

Video Capsule Endoscopy Is Safe and Effective in Pediatric Patients

Wireless video capsule endoscopy (VCE) is a relatively noninvasive imaging modality that provides advanced gastrointestinal imaging for patients with Crohn's disease and other conditions. Few studies have examined pediatric use of this imaging technology. At Digestive Disease Week 2014, Dr Stephen Nanton of the Avera Children's Clinic in Sioux Falls, South Dakota described results from VCE in the diagnosis and management of gastrointestinal disorders in children (Abstract Su1747). The study included 488 consecutive children and young adults (ages 2.5-21.5 years) who had been referred for VCE. The minimum weight requirement was 14.6 kg.

Among the 511 VCE procedures performed, indications included suspected Crohn's disease, anemia, abdominal pain, polyposis syndrome, celiac disease, and gastrointestinal bleeding. A capsule delivery device successfully placed the VCE capsule in the majority of cases. In 25 patients (4.8%), the capsule was placed using laryngoscopic assistance, with 1 failure. In 91 children, the VCE capsule was ingested in the physician's office. The capsule retention rate was 0%.

Twenty-nine children with suspected celiac disease based on elevated tissue transglutaminase antibody levels were examined. Proximal small bowel polyps were found unexpectedly in 7 of these patients (24%). One patient was subsequently diagnosed with Bannayan-Riley-Ruvalcaba syndrome. Classic scalloping of duodenal mucosa, loss of villi, and mosaic patterning were also observed by VCE imaging. Among the 76 patients diagnosed with IBD, 2 were found to have isolated small bowel disease.

In all of the 15 children with Crohn's disease who underwent 2 or more VCE studies to monitor response to therapy, management was modified. In 6 of these patients, VCE observations led to step-up treatment from mesalamine to 6-mercaptopurine. In 8 of 15 patients, VCE results led to the initiation of biologic therapy. In 1 patient, budesonide therapy was initiated for persistent small-bowel Crohn's disease. In 8 of the children with Crohn's disease (53%), endoscopic improvement was documented by VCE, and 15 patients (100%) exhibited clinical improvement after receiving step-up therapy that was initiated in response to the VCE findings. Of the 17 patients found to have polyps in the small bowel, 2 (12%) had been previously diagnosed with familial adenomatous polyposis, 3 (18%) had IBD, and 8 (47%) had celiac disease. For 1 patient, after abdominal computed tomography suggested intussusception, VCE enabled the rare discovery of duodenal windsock diverticulum.

No complications were noted with this approach. The findings underscore the safety and clinical utility of VCE in the pediatric population.

Endoscopic Balloon Dilation Plus Corticosteroid Injection Is Feasible in Pediatric Patients With Crohn's Disease

Crohn's disease is a chronic unremitting immune-mediated inflammation that is complicated in approximately 30% of pediatric patients by the presence of strictures on long-term follow-up. Strictures tend to recur after resection and can require repeated surgical interventions. At Digestive Disease Week 2014, Dr Roberto Gugig of Children's Hospital Central California in Madera, California described results of a prospective pilot study in pediatric patients evaluating the use of endoscopic balloon dilation plus intramural corticosteroid injection, which is currently considered an appropriate conservative therapy in adults (Abstract Su1762). The 12 study participants had a median age of 14.5 years (range, 9-17.5 years), and 8 were male. Strictures were less than 4 cm in length; were located in the esophagus (n=1), antrum (n=1), right colon (n=4), or ileum (n=7); and were inflammatory (n=10) or fibrotic (n=3). In addition to endoscopic balloon dilation, patients received 4-quadrant triamcinolone (40 mg/mL) in aliquots of 0.5 mL to 1 mL. Technical success was defined as the ability of the endoscope to traverse the stricture after dilation.

Twelve patients underwent 15 dilations, with 4 patients (33%) requiring repeat dilations. Technical success was achieved in all patients. Improvement of symptoms was also achieved in all patients. Long-term success, defined as freedom from symptoms for longer than 1 year, was achieved in 9 patients (75%). One patient with fibrotic strictures required surgery, and no endoscopy-related complications or perforations were observed. Dr Gugig concluded that, in select pediatric patients with Crohn's disease and strictures, endoscopic balloon dilation plus corticosteroid injection reduces the need for surgical interventions.

Electroacupuncture Decreases Analgesic Use During Endoscopic Ultrasound

Although electroacupuncture is a part of traditional Chinese medicine, limited data exist on its risks and benefits as an analgesic during endoscopy. At Digestive Disease Week 2014, Dr Anthony Y. Teoh of the Department of Surgery at the Chinese University of Hong Kong in Shatin, Hong Kong described results from a study investigating the efficacy of electroacupuncture in reducing analgesic consumption and diminishing patients' perceptions of procedure-related pain (Abstract Tu2036). The prospective, double-blind, sham-controlled, randomized study included consecutive patients ages 18 to 80 years. All patients were undergoing endoscopic ultrasound for the first time; they were grade 1 or 2 according to criteria from the American Society of Anesthesiologists. Patients received electroacupuncture for approximately 45 minutes prior to the surgical procedure as well as during the procedure. Electroacupuncture was applied to acupoints associated with treating upper abdominal pain and anxiety, including Zusanli (stomach meridian ST-36), Hegu (large intestine meridian LI-4), and Nei guan (pericardium meridian PC-6). Electric stimulation was delivered at a frequency of 2 Hz, with a pulse width of 200 μs, at a stimulation intensity below the level causing discomfort. The primary outcome was the patient-controlled dose of analgesia consisting of propofol and alfentanil. Patient-related secondary outcomes included overall pain score, patient satisfaction, and willingness to repeat the procedure.

Table 2. Electroacupuncture During Endoscopic Ultrasound

	Acupuncture Group (n=32)	Sham Group (n=32)	*P* Value
Number of successful PCSA demands (median and range)	2 (1-17)	10 (1-18)	.001
Total dose of propofol consumed (mg/kg, mean±SD)	0.22±0.17	0.71±0.41	<.001
Patients' pain score (mean±SD)	2.1±2.1	6.2±2.5	<.001
Patients' satisfaction score (mean±SD)	8.7±1.2	7.1±1.9	.002
Patients' willingness to repeat the procedure (yes/no)	15/17	8/24	.05
Endoscopists' satisfaction score (mean±SD)	8.3±1.7	7.3±2.6	.110

PCSA, patient-controlled sedation/analgesia; SD, standard deviation.

Data from Teoh AY et al. DDW abstract Tu2036. *Gastroenterology*. 2014;146(suppl 1).

The study randomized 64 patients evenly into 2 well-balanced arms with similar numbers of patients who underwent radial, linear, or mini-probe examinations. Patients who received active electroacupuncture required a significantly lower dose of propofol ($P<.001$) and requested analgesics significantly less often ($P<.001$; Table 2). The patient pain score was reduced from 6.2 for patients receiving the sham procedure to 2.1 for those receiving electroacupuncture ($P<.001$), and electroacupuncture increased the patient satisfaction score from 7.1 to 8.2 ($P=.002$). Patients in the electroacupuncture arm were also more willing to repeat the procedure ($P=.05$). The endoscopists' satisfaction scores were similar between the 2 arms ($P=.110$). Based on the superior results achieved with active electroacupuncture, the study was terminated early.

L-Menthol Spray Reduces Colonic Peristalsis and Improves the Adenocarcinoma Detection Rate

Although colonoscopy is a preferred method of detecting colorectal neoplasms, colonic peristalsis during the procedure can obscure some neoplasms from view. Intravenous or intramuscular injection of antispasmodic agents can alleviate the problem, but unexpected AEs may result. L-menthol, the major constituent of peppermint oil, can suppress gastric peristalsis. In a topic forum at Digestive Disease Week 2014, Dr Ken Inoue of the OSF Medical Group in Bloomington, Illinois and colleagues presented results of a prospective, single-blind, randomized, placebo-controlled study examining the value of L-menthol during colonoscopy (Abstract 740).

Patients scheduled for colonoscopy were randomized to receive L-menthol (n=118) or placebo (n=108). Patients in the active arm received 20 mL of a 1.6% L-menthol solution sprayed directly on the cecum and through the working channel by means of an endoscope. The L-menthol treatment was repeated if peristalsis resumed. The primary outcome was the difference in the rate of adenoma detection, defined as the proportion of screened subjects in whom at least 1 adenomatous lesion was identified. The secondary outcome was the proportion of patients with no peristalsis. Peristalsis was graded on a scale from 0 (none) to 3 (severe).

Baseline data were similar between the 2 arms. The adenoma detection rate was significantly higher in the L-menthol arm compared with the placebo arm (60.2% vs 42.6%; $P=.0083$). The proportion of patients with no

peristalsis was significantly higher after treatment with L-menthol compared with the placebo group (71.2% vs 30.9%; *P*<.0001). In the L-menthol treatment arm, peristalsis scores were significantly reduced after treatment (*P*<.0001); in contrast, in the placebo group, peristalsis scores did not differ significantly before vs after treatment. No AEs were observed in either arm.

A New Biopsy Technique Improves Diagnosis of Barrett Esophagus

Barrett esophagus is characterized by esophageal goblet cell metaplasia. It is typically diagnosed using the modified Seattle protocol technique, in which 4-quadrant forceps biopsies are taken at sites no further than 2 cm apart throughout the Barrett esophagus segment. However, because this method leaves a large amount of unsampled tissue, areas of advanced dysplasia or neoplasia may remain unexamined. Studies with wide area transepithelial sampling with 3-dimensional analysis (WATS3D) have demonstrated improved detection of Barrett esophagus and dysplasia. The new technique collects a disaggregated tissue specimen from a wide area and surveys the entire thickness of the epithelial section being analyzed, thus including the submucosa.

At Digestive Disease Week 2014, Dr Seth A. Gross of the New York University School of Medicine in New York, New York described a study of this new biopsy technique for Barrett esophagus. The retrospective study estimated the adjunctive yield of WATS3D compared with forceps biopsy across numerous community-based gastroenterology practices (Abstract 371). The study included patients with GERD and proven or possible Barrett esophagus. The upper endoscopies were performed by 28 gastroenterologists. WATS3D biopsies were obtained with the standard 2-brush technique, with additional forceps biopsies obtained afterward during the sample endoscopy. All biopsy samples were analyzed at a central laboratory.

The analysis included 2498 specimen sets. Most of the patients (60%) were female, and the mean age was 55 years (range, 15-97 years). GERD was the most common indication for endoscopy. In 80% of patients, the Barrett esophagus length was less than 3 cm. Forceps biopsy resulted in the identification of Barrett esophagus in 277 cases (15.1%). Dysplasia was seen in 17 patients (4.51% of Barrett esophagus cases and 0.68% of patients who underwent forceps biopsies). Adjunctive use of WATS3D led to the identification of an additional 258 Barrett esophagus cases, increasing the diagnostic sampling yield to 25.4% and representing a 68.4% increase in the identification of this condition. In addition, WATS3D enabled the detection of an additional 10 cases of dysplasia and 1 case of cancer, all of which were missed by forceps biopsy. In total, the use of WATS3D increased the detection of dysplasia and neoplasia by 64.7%, leading to an overall detection rate of 1.12%. Dr Gross and colleagues concluded that the use of WATS3D in community-based gastroenterology practices improves patient care by identifying dysplasia missed by standard forceps biopsy.

Peroral Endoscopic Myotomy and Laparoscopic Heller Myotomy Are Equivalent for Treating Idiopathic Achalasia

Achalasia is a rare primary esophageal disorder marked by the absence of peristalsis and an inability of the smooth muscle fibers of the esophagus to relax. Symptoms may include regurgitation, coughing, choking, and esophagitis. The gold standard surgical treatment for achalasia is laparoscopic Heller myotomy (LHM). Peroral endoscopic myotomy (POEM) is a newer approach that may offer an effective and less invasive alternative. However, no consensus exists regarding which of these 2 therapies provides the greatest safety and efficacy for achalasia patients, and cost comparisons have not been published. At Digestive Disease Week 2014, Dr Vivek Kumbhari of the Johns Hopkins University School of Medicine in Baltimore, Maryland presented results of a retrospective study examining the efficacy, safety, and costs of LHM and POEM in treating patients with idiopathic achalasia (Abstract Tu1354).

This single-center study evaluated consecutive patients who underwent LHM or POEM between 2008 and 2013. All LHMs included a Toupet fundoplication and were performed transabdominally. All POEMs were performed by a single gastroenterologist in the endoscopy unit. Clinical response was defined by symptom improvement and a decrease in Eckardt stage to 0 or 1.

Twenty-one POEM and 66 LHM cases met the inclusion criteria, and baseline demographics and preprocedure characteristics were similar between both groups, as was the myotomy length. Procedure time was significantly curtailed by use of POEM (136 minutes vs 277 minutes; *P*<.01). The 2 procedures yielded similar clinical responses (*P*=.45), at a median follow-up of 2.6 months for POEM and 1.9 months for LHM. Both procedures were associated with similar lengths of hospitalization following surgery (*P*=.08). Rates of mild and moderate AEs were also similar between the 2 groups, and no severe complications were observed. The 2 procedures incurred similar mean total charges for the duration of the hospital stay. Dr Kumbhari and colleagues concluded that POEM and LHM are associated with similar safety, efficacy, and costs.

Underwater Endoscopic Mucosal Resection Is Feasible for Scarred Polyp Removal

Resection of colon polyps often leads to the formation of scar tissue, complicating future surgeries. Recurrence rates exceeding 25% have been reported. Underwater endoscopic mucosal resection effectively removes large colorectal polyps and offers a promising approach for the removal of scarred polyps. At Digestive Disease Week 2014, Dr Chris M. Hamerski of the California Pacific Medical Center in San Francisco, California described results of a study of polyp removal by underwater endoscopic mucosal resection (Abstract Tu1454). The study evaluated the feasibility and efficacy of underwater endoscopic mucosal resection performed at a single center for the removal of polyps 10 mm or larger and characterized by scarring from previous resection attempts. Mucosal resection was performed under full water immersion using a snare. En bloc resection was performed when feasible, and hot biopsy forceps were used to remove any remaining tissue that was not removable by snare.

The study included 58 patients who underwent colonoscopy for endoscopic mucosal resection of a polyp with a prior resection attempt. The mean polyp size was 20 mm (range, 10-20 mm). The polyp locations included the right colon (72%), the rectum (16%), and the descending or sigmoid colon (12%). The median resection time was 5 minutes (range, 1-175 minutes). Forty-three percent of polyps were removed en bloc, with an additional 43% removed in pieces using the snare. Ten percent of cases required additional resection with biopsy forceps, and 1 polyp (2%) required use of argon plasma coagulation. For 1 polyp with significant scarring, complete resection was attempted, but the case was referred to surgery.

The majority of polyps (86%) were adenomas without high-grade dysplasia. Malignancy was observed in 4 polyps (7%); of these, 2 were removed en bloc, and pathology revealed negative margins. The other 2 polyps were surgically examined, and no residual adenoma or cancer was found. Four polyps showed evidence of high-grade dysplasia. Follow-up data were available from 20 patients (34%), at a median follow-up of 26 weeks. One patient (5%) had residual adenoma on follow-up colonoscopy, and 1 patient developed delayed bleeding requiring hospitalization.

Brief Summary about BreathTek UBT

Intended Use

The BreathTek® UBT for *H. pylori* Kit (BreathTek UBT Kit) is intended for use in the qualitative detection of urease associated with *H. pylori* in the human stomach and is indicated as an aid in the initial diagnosis and post-treatment monitoring of *H. pylori* infection in adult patients and pediatric patients 3 to 17 years old. The test may be used for monitoring treatment if used at least 4 weeks following completion of therapy. For these purposes, the system utilizes an Infrared Spectrophotometer for the measurement of the ratio of $^{13}CO_2$ to $^{12}CO_2$ in breath samples, in clinical laboratories or point-of-care settings. The Pediatric Urea Hydrolysis Rate Calculation Application (*p*UHR-CA), provided as a web-based calculation program, is required to obtain pediatric test results.

The BreathTek UBT Kit is for administration by a health care professional, as ordered by a licensed health care practitioner.

Warnings and Precautions

- For in vitro diagnostic use only. The Pranactin®-Citric solution is taken orally as part of the diagnostic procedure and contains Phenylalanine (one of the protein components of Aspartame), 84 mg per dosage unit, and should be used with caution in diabetic patients. (For reference, 12 ounces of typical diet cola soft drinks contain approximately 80 mg of Phenylalanine.)
- A negative result does not rule out the possibility of *H. pylori* infection. False negative results do occur with this procedure. If clinical signs are suggestive of *H. pylori* infection, retest with a new sample or an alternate method.
- False negative test results may be caused by:
  - — Ingestion of proton pump inhibitors (PPIs) within 2 weeks prior to performing the BreathTek UBT. If a negative result is obtained from a patient ingesting a PPI within 2 weeks prior to the BreathTek UBT, it may be a false-negative result and the test should be repeated 2 weeks after discontinuing the PPI treatment. A positive result for a patient on a PPI could be considered positive and be acted upon.
  - — Ingestion of antimicrobials, or bismuth preparations within 2 weeks prior to performing the BreathTek UBT
  - — Premature POST-DOSE breath collection time for a patient with a marginally positive BreathTek UBT result
  - — Post-treatment assessment with the BreathTek UBT less than 4 weeks after completion of treatment for the eradication of *H. pylori*.
- False positive test results may be caused by urease associated with other gastric spiral organisms observed in humans such as *Helicobacter heilmannii* or achlorhydria.
- If particulate matter is visible in the reconstituted Pranactin-Citric solution after thorough mixing, the solution should not be used.
- Patients who are hypersensitive to mannitol, citric acid or Aspartame should avoid taking the drug solution as this drug solution contains these ingredients. Use with caution in patients with difficulty swallowing or who may be at high risk of aspiration due to medical or physical conditions.
- No information is available on use of the Pranactin-Citric solution during pregnancy.
- For pediatric test results, the Urea Hydrolysis Rate (UHR) results must be calculated. The Delta over Baseline (DOB) results are only used to calculate the UHR metrics to determine *H. pylori* infection in pediatric patients. DOB results **cannot** be used to determine the infection status of pediatric patients. Use the web-based *p*UHR-CA (https://BreathTekKids.com) to calculate the UHR.
- Safety and effectiveness has not been established in children below the age of 3 years.

Adverse Events

During post-approval use of the BreathTek UBT in adults, the following adverse events have been identified: anaphylactic reaction, hypersensitivity, rash, burning sensation in the stomach, tingling in the skin, vomiting and diarrhea. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure.

In two clinical studies conducted in 176 (analyzed) pediatric patients ages 3 to 17 years to determine the initial diagnosis and post treatment monitoring of *H. pylori*, the following adverse events experienced by ≥1% of these patients were: vomiting (5.1%), oropharyngeal pain (4.5% to include throat irritation, sore throat, throat burning), nausea (2.3%), restlessness (2.3%), stomach ache/belly pain (1.1%), and diarrhea (1.1%). Most of the adverse events were experienced by patients within minutes to hours of ingestion of the Pranactin-Citric solution.

In another clinical study comparing the UBiT®-IR300 and POCone® in pediatric patients ages 3 to 17 years, the following adverse events were observed among the 99 subjects enrolled: 2 incidences of headache, and 1 incidence each of cough, dry mouth and acute upper respiratory infection.

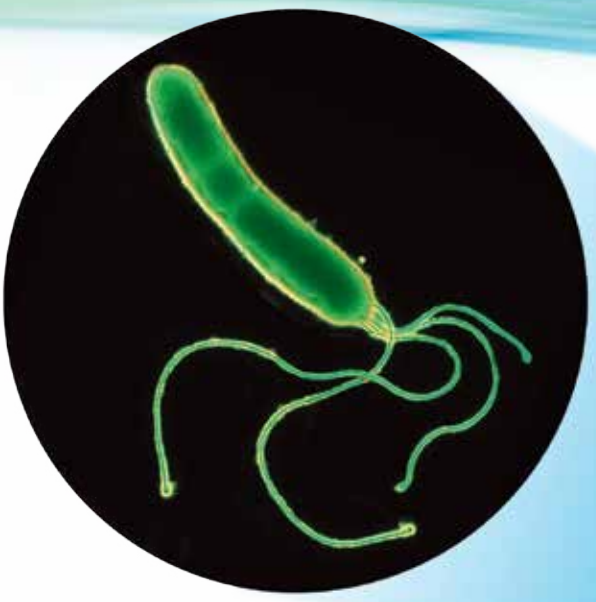
May 2014 05US14EBP1200

Otsuka
Medical Device Division of
Otsuka America Pharmaceutical, Inc.

Urea Breath Test for *H. pylori*
BreathTek®

August 2014 05US14EBP1342

H. pylori
Easy to find.
Hard to kill.



Learn more about the importance of confirming eradication from a leading expert in gastroenterology

Watch *"Helicobacter pylori:* Importance of Appropriate Testing and Management"

Scan this code or visit www.BreathTek.com/confirm

Antibiotic resistance is approaching 25%, increasing the need for eradication confirmation[1]

The prevalence of *H. pylori* in the United States is estimated to be between 30% and 40%.[2] Americans born outside the country and those over the age of 50 years have an even higher prevalence of *H. pylori* (60% and 50%, respectively).[3,4]

While *H. pylori* is relatively easy to find, it can be difficult to eradicate. As many as 1 in 4 patients fail *H. pylori* eradication therapy.[5,6] In addition, a number of controlled trials indicate significant resistance of *H. pylori* to antibiotics in triple therapy.[1] The data suggest that *H. pylori* resistance is on the rise.[1]

BreathTek® UBT for *H. pylori* is an easy and convenient test to confirm *H. pylori* eradication. BreathTek UBT offers excellent sensitivity (96%) and specificity (96%) to confirm eradication in adult patients.[7] BreathTek UBT is a patient-friendly option that may increase compliance. Urea breath test (UBT) methods are recommended by the American College of Gastroenterology over stool testing to confirm *H. pylori* eradication.[1,2,8,9]

Please see BRIEF SUMMARY on adjacent page or visit www.BreathTek.com

References: 1. Vakil N, Megraud F. Eradication therapy for Helicobacter pylori. *Gastroenterology.* 2007;133(3):985-1001. **2.** Chey WD, Wong BCY; Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of Helicobacter pylori infection. *Am J Gastroenterol.* 2007;102(8):1808-1825. **3.** Cardenas VM, Mulla ZD, Ortiz M, Graham DY. Iron deficiency and Helicobacter pylori infection in the United States. *Am J Epidemiol.* 2006;163(2):127-134. **4.** Fee C, Nemer JA. Acute infectious gastrointestinal disorders. *Hosp Physician Emerg Med Board Rev Manual.* 2004;8(pt 1):2-11. **5.** Vakil N, Fendrick AM. How to test for Helicobacter pylori in 2005. *Cleve Clin J Med.* 2005;72(suppl 2):S8-S13. **6.** Chu Y-T, Wang Y-H, Wu J-J, Lei H-Y. Invasion and multiplication of Helicobacter pylori in gastric epithelial cells and implications for antibiotic resistance. *Infect Immun.* 2010;78(10):4157-4165. **7.** Package Insert for BreathTek UBT. Otsuka America Pharmaceutical, Inc; 2014. **8.** Ore L, Hagoel L, Lavi I, Rennert G. Screening with faecal occult blood test (FOBT) for colorectal cancer: assessment of two methods that attempt to improve compliance. *Eur J Cancer Prev.* 2001;10(3):251-256. **9.** Cullen KP, et al. Evaluation of the Helicobacter pylori stool antigen (HpSA) test in routine clinical practice—is it patient friendly? *Ir Med J.* 2002;95(10):305-306.

Urea Breath Test for *H. pylori*

BreathTek®

August 2014 05US14EBP1342