

THE GASTRO & HEP REPORT

Presentation summaries in:

7 GERD

12 Hepatology

17 Endoscopy

19 IBD

21 IBS

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

- The 44th Annual Meeting of the European
Association for the Study of the Liver

April 22–26, 2009

Copenhagen, Denmark

- Digestive Disease Week 2009

May 30–June 4, 2009

Chicago, Ill.

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Presentations in GERD

Health-Related Quality of Life Improves in Most GERD Patients With Routine Care Over a 5-Year Period

Gastroesophageal reflux disease (GERD) is associated with substantial reductions in health-related quality of life (HRQoL). Nocon and associates analyzed the patterns of change in HRQoL during 5 years of follow-up in patients under routine care. In 2000, 6,215 GERD patients were enrolled in the Progression of GERD (ProGERD) study. During follow-up, patients received any medication considered necessary for the treatment of GERD. HRQoL was assessed yearly using the Short-Form 36 and the disease-specific Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaires. After 5 years, data on HRQoL were available for 4,597 patients. HRQoL improved from baseline and remained well above baseline levels in the following years. Clinically meaningful improvement of mean scores for QOLRAD domains of emotional distress, sleep disturbance, food/drinking problems, and vitality was observed in more than 60% of patients. A decrease in scores was reported by only 3–5% of patients. According to multivariate analysis, this deterioration was associated with a higher reflux symptom load and the presence of nighttime heartburn.

Dual Delayed-Release Proton Pump Inhibitor Shows Dosing Flexibility

Administering some proton pump inhibitors (PPIs) with food can reduce their absorption and bioavailability. Dexlansoprazole is a PPI with a dual delayed-release formulation that prolongs plasma drug concentrations. Lee and colleagues evaluated the effects of time-of-day dosing on the pharmacokinetics and pharmacodynamics after once-daily administration of dexlansoprazole. Forty-eight healthy subjects received dexlansoprazole 60 mg orally once daily for 5 days at four different times of day. The researchers compared dosing 30 minutes before breakfast (Regimen A) with dosing before lunch (B), dinner (C), and an evening snack (D). They measured plasma drug levels and intragastric pH levels. Forty-four subjects completed all regimens. The 90% confidence intervals

for the ratios of dexlansoprazole maximum concentration and the area under the curve (AUC) for before-breakfast dosing versus other times of the day were within the bioequivalence limits. The observed difference in mean 24-hour pH between Regimen A and Regimens C or D was less than 0.1 and not statistically significant; however, a small (0.2) but statistically significant difference was seen between Regimens A and B. The observed differences in the percentage of time with a pH greater than 4 over 24 hours between Regimens B or C versus Regimen A were both less than 3% and not statistically significant; a small (7%) but statistically significant difference was seen between Regimens A and D. The researchers concluded that there were little to no differences in systemic exposure or in mean 24-hour intragastric pH and the percentage of time with a pH greater than 4 when dexlansoprazole was administered before lunch, dinner, or a snack compared with breakfast.

Metoclopramide Stimulates Duodenal Pressure Waves and Propagates Pressure Sequences

Because the contribution of small intestinal motor activity to nutrient absorption is poorly defined, Kuo and associates set out to investigate the effects of the prokinetic drug metoclopramide on duodenal motility, flow events, and glucose absorption. Eight healthy volunteers were given metoclopramide or saline (one on each of two study days) intravenously, followed by an intraduodenal glucose infusion. The researchers measured glucose concentrations in the blood and monitored pressure waves and flow events in the duodenum, and compared them across the 2 study days. They found that metoclopramide increased the total number of duodenal pressure waves (601 ± 128 vs 328 ± 34 for saline) and propagated pressure sequences (94 ± 22 vs 43 ± 12 for saline). However, the total number of duodenal flow events and the level of glucose absorption were not found to be different between the 2 study days. The authors concluded that duodenal flow events are a better indicator of glucose absorption than pressure waves, and may be useful to measure in future studies of nutrient absorption.

Wireless pH Monitoring A Safe Alternative to Catheter-Based pH Systems in an Asian Cohort

Traditional catheter-based esophageal pH monitoring is limited by patient discomfort and inconvenience. The wireless monitoring system requires attachment of a capsule in the esophageal lumen to record ambulatory pH levels. Although this system has been validated, its usefulness in specific patient populations is still under evaluation. Ang and colleagues studied the efficacy of capsule monitoring in patients with suspected GERD in a multiracial Asian cohort by reviewing the records of patients who underwent pH monitoring from January 2004 through October 2008. A total of 55 and 47 patients underwent wireless and catheter-based monitoring, respectively. Although all patients completed the capsule monitoring study, 4 (8.5%) patients failed completion of the catheter recording due to intolerance. Abnormal total acid exposure times (AET) were recorded for 20 (36%) of the wireless patients and 16 (34%) of the patients who underwent catheter monitoring. A positive reflux-symptom association was noted, despite normal AET, in 7 (12.7%) and 9 (19.1%) of patients who underwent wireless and catheter monitoring, respectively. The researchers concluded that the wireless capsule was well tolerated and that the prevalence of abnormal acid exposure and positive reflux-symptom association was similar using both methods.

Considering Surgical Therapy in GERD Patients with Extraesophageal Symptoms

Klochan and associates note that management of patients with extraesophageal reflux (EER) symptoms that are unresponsive to acid suppression remains a controversial topic. Referral for fundoplication in cases of abnormal nonacid reflux, based on impedance monitoring, is recommended but not uniformly practiced in the community and referral criteria vary among practitioners. The authors aimed to determine if subjective patient information (eg, complaints of heartburn or regurgitation) or objective data (degree of reflux

or symptom index [SI]/symptom probability analysis [SAP], esophagogastroduodenoscopy [EGD], or manometric findings) can predict surgical outcomes.

The study population consisted of patients with persistent EER symptoms who were referred for fundoplication and who had undergone impedance pH monitoring on therapy with PPI, off therapy with wireless pH, EGD, and manometry. Abnormal acid reflux (% time pH <4) was the only pre-requisite for fundoplication. Off-therapy presence of typical GERD symptoms (heartburn or regurgitation) as well as endoscopic, manometric, impedance and pH parameters (SI and SAP) on and off therapy were used to determine the best predictor of improvement. Outcome was assessed based on primary symptom improvement (score 0–2).

Eighteen patients (mean age 50 y; 55% male; 78% white) underwent fundoplication from 2006 to 2008. Symptoms included cough (50%), asthma (33%), throat symptoms (17%), and regurgitation (6%). Heartburn was reported among 67% and regurgitation among 56% of patients at baseline.

All had abnormal off-therapy pH monitoring. On impedance monitoring, 44% had positive SI, 50% had positive SAP, and 67% experienced an abnormal number (>48) reflux episodes. EGD tested abnormal in 59% (60% hiatal hernia, 10% esophagitis, 20% columnar mucosa). Motility was reported abnormal in 72% of patients.

Median follow-up was at 12 months (range: 2–27 mo). At this time, 28% of patients had experienced no change, 39% had improved, and 33% had resolved all symptoms. Neither SAP, SI, number of reflux events (acid or non-acid), nor percent time of pH less than 4 predicted response to therapy. However, presence of baseline heartburn or regurgitation was statistically ($P=0.02$) associated with response to therapy. The authors concluded that baseline presence of both heartburn and regurgitation in patients with EER symptoms refractory to PPI therapy is the only predictor of outcome for fundoplication and that consideration of both clinical symptoms and objective data (baseline abnormal pH) may be the best predictor of reflux contribution to extraesophageal symptoms.

Presentations in Hepatology

Rifaximin Reduces the Risk of Hospitalizations in Patients with a History of Hepatic Encephalopathy

Hepatic encephalopathy (HE) is defined by a set of neuropsychiatric abnormalities caused by liver dysfunction and resultant accumulation of systemic ammonia in patients with end-stage liver disease. The standard treatment for HE is administration of oral lactulose. Rifaximin is a gut-selective antibiotic that has been shown to reduce the frequency and duration of hospitalizations in patients with HE. In a phase III trial, rifaximin demonstrated significant reduction in the risk of breakthrough HE versus placebo in the overall intent-to-treat population by 58% (hazard ratio, 0.421; $P < .0001$). Neff and associates performed a sub-analysis examining the efficacy of rifaximin in reducing the risk of HE-related hospitalizations. A total of 299 patients with a history of 2 or more episodes of HE within 6 months prior to screening were enrolled. All patients were in remission for HE at the time of the trial. Patients were randomized to receive either rifaximin 550 mg twice daily for 6 months, or placebo. Continued therapy with lactulose was permitted in both arms of the study. During the treatment period, patients were assessed in the clinic and via telephone, with a key secondary endpoint being the time to first HE-related hospitalization. At 6 months, 16% of patients on rifaximin experienced HE-related hospitalizations, compared with 26% of those receiving a placebo ($P = .04$). The researchers found that the treatment of only 9 patients with rifaximin was required to prevent one case of HE-related hospitalization.

Entecavir Maintains a 6-Year Genetic Barrier to HBV Resistance in Nucleoside-Naïve Patients

Entecavir (ETV) is an oral antiviral agent used in the treatment of hepatitis B virus (HBV) infection. Previous studies have determined that it provides potent viral suppression and a high genetic barrier to resistance through 5 years of treatment. Studies have also shown a reduced

barrier to resistance in lamivudine (LVD)-resistant patients. In a study by Tenney and colleagues, all patients receiving continuous therapy in registrational trials were monitored for resistance through year 6. The researchers performed sequencing on serum samples with detectable HBV DNA at each cross-sectional end-of-year analysis, or with viral breakthrough at any time, or at discontinuation from the study with detectable HBV DNA. The cumulative probabilities of resistance were determined through year 6. In years 1 through 6, respectively, 663, 278, 149, 120, 108, and 99 nucleoside-naïve patients were treated and monitored, with 94% in year 6 having HBV DNA of fewer than 300 copies/mL. The cumulative probability of genotypic entecavir resistance in nucleoside-naïve patients remained at 1.2% through 6 years. Among LVD-refractory patients treated with ETV, 187, 146, 80, 52, 33, and 29 were monitored in years 1 through 6, respectively. The cumulative probabilities of genotypic ETV resistance at years 1 through 6 were 6%, 15%, 36%, 47%, 51%, and 57% respectively. The probability of virological breakthrough with ETV resistance was 50% through year 6. Among the 74 LVD-refractory patients who achieved undetectable HBV DNA on ETV, 5 subsequently developed ETV resistance. The investigators concluded that ETV resistance remains rare through 6 years of treatment in nucleoside-naïve patients. They noted that LVD-resistant HBV has a reduced resistance barrier to ETV and that patients with this type of HBV may benefit from add-on or combination therapy.

Induction Dosing of Peginterferon Alfa-2a With Standard Ribavirin Therapy Enhances Early, But Not Sustained Virological Responses in HCV Genotype 1 Patients

Genotype 1 chronic hepatitis C virus (HCV) infections are often difficult to treat because they are the most resistant to standard therapies. The CHARIOT study tested the hypothesis that double-dose peginterferon alfa-2a for the first 12 weeks of treatment increases early virological response (EVR) and improves sustained

virological response (SVR) in treatment-naïve patients with chronic hepatitis C genotype 1. Roberts and associates reported on this multicenter, open-label study in which 896 patients were stratified by baseline HCV RNA level. Participants were randomized to receive either a standard dose of peginterferon for 48 weeks (180 µg/week), or induction dosing (a double dose for 12 weeks, followed by a standard dose for 36 weeks). All patients received ribavirin at 1,000–1,200 mg/day over the 48-week period. Of the total patients enrolled, 871 were evaluable for the intention-to-treat analysis. Virological responses at weeks 4 and 12 were significantly higher among the patients receiving induction therapy, but the SVR rate was not significantly different between the groups receiving high-dose (53%) and standard (50%) therapy. The early virological advantage provided by induction therapy was partially diminished by week 24 and lost by the end of therapy. The frequency of serious adverse events and discontinuations were similar in both groups. However, dose modification, reduction in weight and appetite, diarrhea, and grade IV neutropenia were higher in the induction arm. The researchers noted that although high-dose induction therapy was well tolerated and enhanced EVR rates, it did not increase SVR. They concluded that more research is needed to evaluate the benefit of enhanced early responses in future treatment paradigms.

Adding Telaprevir to Standard Therapy Improves Sustained Virological Response in HCV Genotype-1-Infected Patients

Manns and colleagues conducted a randomized, placebo-controlled phase II study to assess the efficacy and safety of telaprevir (T) in the treatment of patients who previously failed treatment with peginterferon-alfa-2a (P) and ribavirin (R). Patients were randomized to receive one of four treatment regimens: T/PR for 12 weeks, then PR for 12 weeks (T12/PR24); T/PR for 24 weeks, then PR for 24 weeks (T24/PR48); T/P for 24 weeks (T24/P24); or placebo/PR for 24 weeks, then PR for 24 weeks (PR48). Of the 453 patients included in the intention-to-treat analysis, 235 (52%) completed the assigned treatment. Eleven (10%), 29 (25%), 10 (9%), and 5 (4%) patients discontinued due to adverse events in T12/PR24, T24/PR48, T24/P24, and PR48, respectively. The researchers found that SVR rates in all treatment groups receiving T were significantly higher than in groups that did not receive it. The general safety profile of T12/PR24 was similar to that observed in treatment-naïve patients. The higher relapse rate in the T12/PR24 compared with T24/PR48 indicated to

researchers that a 48-week course of PR therapy may be warranted in treatment-experienced patients. A phase III study evaluating two T12/PR48 regimens is currently underway.

Tenofovir Disoproxil Fumarate Shown to Be Safe and Effective at 2 Years in Patients with HBV-Induced Cirrhosis

Tenofovir disoproxil fumarate is a nucleotide analogue reverse transcriptase inhibitor that was recently approved for the treatment of chronic HBV. Buti and associates performed an efficacy and safety analysis of patients in two phase III registration trials with cirrhosis who received tenofovir for 96 weeks. In both trials, patients were randomized to receive tenofovir 300 mg or adefovir 10 mg once daily for 48 weeks. If a biopsy was performed at week 48, patients were eligible to receive open-label tenofovir for an additional 7 years. Patients with confirmed HBV DNA above 400 copies/mL had the option to initiate combination emtricitabine with tenofovir after week 72. Of the 426 patients originally randomized to tenofovir, 81 (19%) were cirrhotic, with 47 hepatitis B e antigen-negative (HBeAg-) and 34 HBeAg-positive (HBeAg+). The median baseline HBV DNA was 7.58 log₁₀ copies/mL with an ALT of 92 U/L. Similar proportions of cirrhotic and non-cirrhotic patients suppressed HBV DNA to less than 400 c/mL at week 96: 90% versus 85% in the intention-to-treat analysis and 97% versus 95% (observed). Among patients remaining on treatment, 83% of cirrhotic and 78% of non-cirrhotic patients had normal ALT at week 96. Of 29 cirrhotic HBeAg+ patients with serology results at week 96, 9 seroconverted to anti-HBe (31%) and 2 seroconverted to anti-HBs (hepatitis B surface antigen). Grade 3 and 4 adverse events occurred in 11% of cirrhotic and 13% of noncirrhotic patients, serious adverse events occurred in 15% and 9%, and Grade 3/4 laboratory abnormalities in 31% and 23%, respectively. The researchers concluded that the efficacy and safety of tenofovir at 96 weeks was not influenced by the existence of cirrhosis at the onset of therapy, and that its tolerability was acceptable in both cirrhotic and non-cirrhotic patients.

Tenofovir Disoproxil Fumarate Effective in Lamivudine-Experienced Patients

As described above, tenofovir disoproxil fumarate is a recently approved antiviral therapy for the treatment of chronic hepatitis B infection. Tenofovir has also demonstrated activity against lamivudine-resistant HBV. Manns and colleagues considered treatment response to tenofovir

for a subset of patients previously treated for more than 12 weeks with lamivudine or emtricitabine (LAM-experienced), compared to response in LAM-naïve patients.

In Studies 102 and 103, HBeAg⁻ or + chronic hepatitis B patients were randomized 2:1 to double-blind, once daily tenofovir 300 mg or adefovir dipivoxil 10 mg. After 48 weeks, patients with a week 48 biopsy continued on open-label tenofovir for up to 7 additional years. Across both studies, a total of 426 patients were initially randomized to tenofovir (51 LAM-experienced patients and 375 LAM-naïve patients).

A total of 49 LAM-experienced patients and 350 LAM-naïve patients completed 96 weeks of tenofovir treatment. The majority of LAM-experienced patients enrolled were HBeAg⁻ (n=41). A similar proportion of patients achieved viral suppression (HBV DNA <400 c/mL; 69 IU/mL) at week 96 in the LAM-experienced versus LAM-naïve group: 92% versus 84% (intent-to-treat) and 98% versus 95% (on-treatment). Ninety-one percent of LAM-experienced patients and

77% of LAM-naïve patients had normal ALT at week 96. No LAM-experienced patient achieved HBsAg loss. No HBV pol/RT amino acid substitutions associated with tenofovir resistance were detected through 96 weeks of tenofovir monotherapy in LAM-experienced patients.

During year 2, no LAM-experienced patient experienced a serious adverse event or discontinued for an adverse event. Five patients had new G3-4 laboratory abnormalities; serum lipase (4%) was the only abnormality occurring in more than 1 patient (n=2). During open-label tenofovir treatment, no LAM-experienced patient treated for 96 weeks had a confirmed decrease in creatinine clearance less than 50 mL/min, increase in creatinine of 0.5 mg/dL or more, or a graded serum creatinine abnormality. The authors concluded that the safety, efficacy, and resistance analysis results for 96 weeks of tenofovir treatment were similar in LAM-experienced and LAM-naïve chronic HBV patients. Open-label follow-up of these patients is ongoing.

Presentations in Endoscopy

Double-Balloon Endoscopy Superior to Other Methods in Detecting Crohn's Disease Activity in the Small Bowel

Wiarda and colleagues compared imaging via magnetic resonance enteroclysis (MRE) and wireless capsule endoscopy (WCE) with double-balloon enteroscopy (DBE) to measure disease activity in patients with suspected or known Crohn's disease (CD) of the small bowel. In the COMRADE study, 40 patients with suspected or known CD first underwent MRE, followed by WCE and DBE. Thirteen patients (34%) with high-grade stenosis at MRE did not receive WCE. DBE was performed via a proximal and distal approach in 19 (48%) patients, and via distal approach only in the remainder of patients. In 2 patients, DBE was inconclusive due to a failed distal small bowel intubation and both patients were excluded from further evaluation. DBE diagnosed active CD in 20 patients (52.6%) and disease activity was defined as mild, moderate, and severe in 10, 6, and 4 patients respectively. DBE showed high-grade stenosis in 8 (62%) of 13 patients with suspected stenosis at MRE. In 2 (15%) patients, DBE did not visualize the segment with signs of stenosis at MRE. In the remaining 3 (23%) patients, the MRE diagnosis of small bowel stenosis was refuted by DBE. The overall sensitivity and specificity for detection of Crohn's activity for MRE was 88% and 76%, respectively. Sensitivity and specificity for WCE was 75% and 76%, respectively. WCE missed all cases with moderate to severe activity, and was complicated by capsule retention in 1 patient. DBE allowed for proper small bowel assessment in nearly all patients in the study. Although MRE outperformed WCE, it also overdiagnosed stenosis. The authors concluded that the high prevalence of stenosis in this population, combined with the insufficient sensitivity of WCE for detection of Crohn's activity, limit the applicability of WCE in patients with suspected or known CD.

Chromoendoscopy Provides Effective Detection of Dysplasia in High- and Low-Risk Colitis Patients

Patients with long-standing ulcerative or Crohn's colitis are at increased risk for colorectal cancer. Non-dye tar-

geted and random biopsies are the mainstay of cancer surveillance, but newer methods are available, including chromoendoscopy, which involves the use of dye stains to enhance endoscopic imaging. Katz and associates from the Mount Sinai Chromoendoscopy Study Group have previously reported the benefits of chromoendoscopy as compared with traditional detection techniques. In a new analysis of their data, the researchers sought to determine whether the benefits of chromoendoscopy extend to patients at low risk of dysplasia, or whether its benefits are confined to high-risk patients. The researchers analyzed the results of their previous prospective endoscopic study that compared chromoendoscopy and non-dye targeted and random biopsies. They divided the study subjects into low- and high-risk categories. The high-risk group included those with previous dysplasia, adenoma, or a history of primary sclerosing cholangitis, whereas the low-risk group included all other patients. Using this stratification system, 50 patients were defined as high risk and 52 as low risk for dysplasia. The high-risk patients were found to have a higher number of dysplastic lesions using all three techniques (13 patients vs 4 patients, $P=.017$). Non-dye targeted biopsies revealed 6 patients with dysplasia in the high-risk group and 2 in the low-risk group ($P=.023$). Random biopsies showed 3 patients with dysplasia in the high-risk group versus 2 in the low-risk group, although the results were not found to be statistically significant. The researchers found that 4 out of 6 patients with dysplasia in the low-risk group were detected only with dye-targeted biopsies. In this study, chromoendoscopy resulted in improved detection of dysplasia in both high- and low-risk patients. The investigators concluded that chromoendoscopy should be considered the preferred clinical practice for detecting dysplasia in patients at all level of risk.

Ten-Year Study Reports 6% Incidence of Unplanned Hospital Admissions Within 30 Days After ERCP

The complications of endoscopic retrograde cholangiopancreatography (ERCP) include bleeding, infection, and pancreatitis. Although the incidence of complications is estimated at about 5%, to date, there have been

no population-based studies to track it. A retrospective cohort study by Coelho-Prabhu and colleagues sought to determine the utilization of ERCP and the incidence of inpatient admissions within 30 days after the procedure. The researchers studied billing records of the Mayo Clinic in Rochester, Minnesota, for all patients age 18 years and older from Olmstead County who underwent ERCP between January 1, 1997 and December 31, 2006. Over the 10-year period, 832 county residents underwent 1,079 ERCPs, for an average incidence of 86.32 ERCPs per 100,000 persons per year. Of the total number of ERCPs, 355 (32.9%) were performed as inpatient procedures, and 888 (82.3%) were performed as therapeutic procedures. The most common indications for ERCP were calculus of the bile duct (16.4%), obstruction of the bile duct without calculus or cholangitis (12.4%), and pancreatic disease (7.6%). Admission to the hospital within 30 days of the procedure occurred in 264 (25%) cases. Of these, 101 (38.3%) were emergent and 163 (61.7%) were elective. The researchers determined that 69 admissions were definitely or possibly related to ERCP procedures, reflecting a 6.4% incidence of unplanned re-admissions related to ERCP, a rate that is similar to those found in previous studies. The most common discharge diagnoses for these readmissions were acute pancreatitis (2.5%), bacteremia and cholangitis (1.3%), and bleeding (0.8%).

Utility of Wireless Capsule Endoscopy in Ulcerative Colitis Assessment

Among the approximately 10–15% of patients with colitis who are classified as indeterminate due to mixed features at diagnosis or during follow-up, determination of the optimal treatment course can be challenging. Medical therapies that provide good efficacy in ulcerative colitis (UC) can be less useful in CD. Further, patients thought to have UC can develop CD after surgery.

WCE provides a highly sensitive examination of the small bowel, and has been shown to have superior yield

in known or suspected CD, but has not been studied prospectively in UC. Rubin and colleagues conducted a prospective study, seeking to determine the prevalence of small bowel findings with WCE in adult patients with a clinical diagnosis of UC.

Patients with clinical, endoscopic, and histologic evidence of UC and no evidence of terminal ileitis (by ileoscopy or radiographic study) underwent WCE. Disease activity was assessed using the Simple Clinical Colitis Activity Index (SCCAI) and serologic testing was performed. Two experienced examiners blinded to patient history independently assessed the WCE findings. Discrepancies were resolved by meeting and review. Small bowel findings were converted to Lewis Scores (<135 is normal), and compared to SCCAI and serology results.

Of the 36 patients who met screening criteria and participated in the study, 19 (53%) were male, 24 (67%) were non-smokers, 7 (19%) were ex-smokers, and 5 were smokers of less than 1 pack per day. Median patient age was 43 years (range: 18–78 y), with median age of onset of 29 years (12–54 y) and median duration of disease of 10 years (0–37 y). Among the patients included, 24 had been diagnosed with pancolitis, 11 with left-sided disease, and 1 with proctitis. The median SCCAI score was 5 (1–13) and 14 patients (39%) had a score greater than 7. Median small bowel transit time was 199.5 min (65–374 min). No patient had an abnormal Lewis Score (mean score=1.2 [SD 5]), but 2 patients had a single pinpoint erosion and 1 patient (with prior negative ileoscopy) had an ileal ulcer of less than one fourth of the lumen. SCCAI did not correlate with these findings and review of individual titers did not change this assessment.

The authors concluded that in this series of well-defined adult UC patients with various degrees of clinical activity, WCE and Lewis Scoring did not identify small bowel findings of significance and did not change the diagnosis in 97% of cases. Thus, in patients with a well characterized UC diagnosis, further confirmation via WCE may not be cost effective or necessary.

Presentations in IBD

Persistence in 5-Aminosalicylic Acid Therapies

The lack of patient persistence is a serious issue in the administration of medical therapies for the treatment of inflammatory bowel disease (IBD). The chronic nature of both the disease and therapy and the high pill burden associated with most 5-aminosalicylate (5-ASA) drugs are thought to be the main factors causing low persistence. In a recent study, Kane and colleagues examined patient prescription and refill records for 5-ASA therapy from March to September 2007. The researchers included prescriptions for three mesalamine formulations: MMX mesalamine, delayed-release mesalamine, and controlled-release mesalamine in 250 or 500 mg doses. They also examined records for prescriptions of balsalazide, a mesalamine prodrug. Patients were defined as “continuing” therapy if they refilled all their prescriptions within a time frame of up to twice the duration of their prescription. They were defined as “restarting” if they refilled their prescription after this time. After one year, 20% of patients receiving MMX mesalamine were continually persistent compared with 9% receiving delayed-release mesalamine, 7% (250 mg) and 10% (500 mg) receiving controlled-release mesalamine, and 10% receiving balsalazide. Persistence was highest (21%) in the largest MMX subgroup (41–55 years old), significantly higher than the equivalent subgroups using delayed-release (9%) or controlled-release (9%) mesalamine. Patients receiving MMX mesalamine also had the highest persistence when both continuing and restarting patients were included in the analysis. They received significantly more days of therapy (136) and collected the highest number of prescriptions (nearly 4.5 per patient). In contrast, in the largest treatment group—those receiving delayed-release mesalamine—patients collected an average of 2.7 prescriptions and received a mean 86 days of therapy. The authors concluded that the lower pill burden and once-daily dosing of the MMX formulation may contribute to the higher persistence found in this population.

Higher Dose of Delayed-Release Mesalamine Beneficial in Previously-Diagnosed UC Patients

Although mesalamine treatment is considered the first-line therapy in mild-to-moderate UC, there is some debate over the selection of patients who would benefit from a higher initial induction dose. Sandborn and associates analyzed data from three phase III trials (ASCEND I, II, and III) to compare the benefit of induction dosing in previously diagnosed and newly diagnosed patients with moderately active UC. They compared the efficacy of delayed-release mesalamine at doses of 4.8 g/day and 2.4 g/day in these patients. The investigators defined “previously diagnosed” as a duration of more than one month, and “newly diagnosed” as a duration of one month or less. The primary endpoint was treatment success defined as improvement from baseline on the Physician’s Global Assessment, with no worsening in any individual clinical assessment. The results of the study showed that previously diagnosed patients with moderately active UC responded significantly better to 4.8 g/day compared with 2.4 g/day, whereas response was similar for the two dosing levels in the group with newly diagnosed UC.

Patient’s Functional Assessment Provides Insight Into Onset of Action of Delayed-Release Mesalamine for Ulcerative Colitis

Most UC trials focus on symptomatic and endoscopic improvement at certain time points, which limits the ability to address patient perceptions of onset of action. Sninsky and Ramsey performed an analysis of data from the ASCEND I and II trials to evaluate Patient’s Functional Assessment (PFA) of the onset of action of delayed-release mesalamine 2.4 g/day (400 mg tablets). The researchers assessed PFA on a 4-point scale, where 0 indicates “feeling generally well” and 3 indicates “feeling terrible.” Feeling “better” was defined as a decrease from the baseline of one or more points in the assessment. A

total of 687 patients were randomized in the 2 studies, of whom 349 received the 2.4 g/day dose. The median time to feeling “better” or “generally well” was 3 days (95% confidence interval [CI], 2–3) and 7 days (95% CI, 5–8), respectively. The median time to improvement or resolution of symptoms was 5 days (95% CI, 4–5) and 10 days (95% CI, 8–13), respectively, for rectal bleeding, and 5 days (95% CI, 4–5) and 11 days (95% CI, 8–15) for stool frequency. The authors concluded that delayed-release mesalamine at 2.4 g/day helps mildly to moderately active UC patients feel better quickly. They noted that PFA is important because it reflects patients’ perceptions of improvement without requiring interpretation by healthcare professionals.

SONIC Extension Study Shows Positive Outcomes for Combination Therapy

The Study of Biologic and Immunomodulator Naïve Patients in Crohn’s Disease (SONIC) found that rates of corticosteroid-free clinical remission and mucosal healing at 26 weeks were significantly higher for infliximab administered in combination with azathioprine versus either infliximab or azathioprine alone. The SONIC study also provided an extension period, with an option for patients to continue through week 50. Sandborn and associates reported that 280 (55%) of the 508 patients in the main study entered the extension study. At week 50, 46.2% of the overall study patients were in steroid-free remission with combination therapy, 34.9% with infliximab monotherapy, and 24.1% with azathioprine monotherapy ($P<.001$ for combination therapy vs azathioprine; $P=.028$ for infliximab vs azathioprine; $P=.035$ for combination therapy vs infliximab). The proportion of patients enrolled in the study extension who were in steroid-free remission at week 50 was 72.2% on combination therapy, 60.8% on infliximab monotherapy, and 54.7% on azathioprine monotherapy

($P<.010$ for combination therapy vs azathioprine; $P=.324$ for infliximab vs azathioprine; $P=.065$ for combination therapy vs infliximab). The proportion of patients with serious infections was similar in all treatment groups, and no new opportunistic infections, malignancies, or deaths occurred during the study extension. The researchers concluded that patients treated with infliximab plus azathioprine or infliximab monotherapy are more likely to achieve long-term steroid-free remission than those receiving azathioprine alone.

Certolizumab Pegol Effective in Anti-TNF-Experienced Patients

Certolizumab pegol (CZP) is a biologic therapy for the treatment of CD, which acts as an antagonist of tumor necrosis factor α . The phase IIIb WELCOME study included a 6-week open label induction period followed by a 20-week double-blind maintenance phase to evaluate CZP efficacy and tolerability in patients with moderate to severe CD who had experienced secondary failure to prior therapy with infliximab. Patients with a CD activity index score of 220–450, who had previously responded to infliximab but were no longer responding, or who had developed intolerance, received open-label CZP at weeks 0, 2, and 4. In all, 539 patients enrolled in the study, with a mean of 9 (SD 7.9, range 1–51) previous infliximab infusions. Three hundred and three patients (56.2%) discontinued due to a lack of response to infliximab, 198 (36.7%) discontinued because of infusion reaction only, 35 (6.5%) because of a combination of both, and 3 (0.6%) for other reasons. The researchers found that CZP 400 mg was efficacious in rapidly inducing a clinical response in patients with moderate-to-severe CD who had failed treatment with infliximab, regardless of the dose regimen of the infliximab infusion. CZP was well tolerated and no new safety signals were observed.

Presentations in IBS

Abnormal Lactulose Breath Test Results May Be Explained by Transit Time to Cecum

Recent reports suggest that up to 80% of irritable bowel syndrome (IBS) patients have small intestinal bacterial overgrowth (SIBO). However, these reports are based on results of the lactulose hydrogen breath test (LHBT). Yu and associates hypothesized that the interpretation of the LHBT has been misleading and that results reflect transit time in the small intestine rather than bacterial overgrowth. To test this hypothesis, they performed combined LHBT and scintigraphic oro-cecal transit studies in IBS patients to determine whether the rise in hydrogen in the LHBT occurred before or after a test meal reached the cecum. After an overnight fast, study participants provided a baseline hydrogen breath sample, then ingested a test meal radio-labeled with Tc99. Abdominal images were recorded every 10 minutes for 3 hours, and at the same time, breath samples were collected and analyzed for hydrogen levels. Twenty-six Rome II-designated IBS participants were enrolled in the study. At the time of the study report, 13 subjects had completed the study, 5 had dropped out, and 8 were awaiting complete analysis of test results. Nine (69%) patients with complete results met the criteria for an abnormal LHBT. Of these, 7 had diarrhea-predominant IBS (IBS-D), 1 had alternating symptoms, and 1 had constipation-predominant IBS (IBS-C). In 8 patients, the Tc99 reached the cecum before the LHBT results became abnormal. The median time for the test meal to reach the cecum in these patients was 40 minutes (with a range of 10–70 minutes), whereas the median time for an abnormal LHBT was 65 minutes (with a range of 40–150 minutes). One patient had an abnormal LHBT result before the test meal reached the cecum. The investigators concluded that most of the abnormal LHBT results in IBS patients can be explained by transit to the cecum rather than SIBO.

Phase IIb Study Shows Efficacy of Linaclotide on Symptoms of Constipation-Predominant IBS

Linaclotide is an investigational, minimally absorbed agent that has been shown to reduce visceral pain and

promote intestinal secretion and colonic transit in animal models of IBS. It is the first in its class of guanylate cyclase-C agonists for IBS-C. In a phase IIb study, linaclotide was shown to improve abdominal symptoms, bowel habits, and global assessments in patients with IBS-C over a 12-week treatment period. In a recent post-hoc analysis of the phase IIb results, Lembo and colleagues sought to determine the time to onset of the drug's effect on symptoms. This multicenter study of 420 patients was randomized, double-blinded, and studied a range of doses: 75, 150, 300, and 600 µg, compared with a daily placebo. The researchers found that within the first week of treatment, linaclotide significantly improved patients' abdominal symptoms, bowel habits, and global assessments. The correlation between Week 1 abdominal symptoms was high (for pain and discomfort, $r=0.88$; bloating with abdominal pain and discomfort, $r=0.69$ and 0.76 , respectively). Linaclotide was well tolerated, with diarrhea found to be the most common adverse event.

ROME Foundation Committee Tests IBS Trial Endpoints

Controversy currently exists regarding the adequacy of some IBS trial endpoints. Binary patient-reported outcomes (PROs), such as "adequate relief," may fail to detect minimal clinically important differences (MCIDs) in symptom improvement, and there may be a need to tailor endpoints based on IBS subtype. Members of the ROME Foundation Endpoints Working Group performed a meta-analysis of clinical trials in order to compare binary PROs with a linear severity scale defining a treatment response over time as an improvement of 50% or more. The investigators pooled patient-level data comprising 12 IBS trials and 10,066 patients. Each study included baseline and end-of-study symptom profiles and an end-of-study binary global endpoint. The researchers developed harmonized T-scales for each symptom (mean=100, SD=10) across trials. For the 50% improvement criterion, they adopted abdominal pain intensity as a surrogate for symptom severity, and defined responders as those improving more than 50% over baseline on the pain T-scale. They defined MCID as an improvement of at

least 5 points in the scale score. After evaluating the 9,044 evaluable study subjects, the investigators found that both endpoints identified statistically significant differences in the proportion achieving an MCID for pain, bloating, and stool frequency. However, consistency, urgency, and incomplete evacuation were identified in IBS-D patients only. The proportion of patients achieving MCID was considerably higher in IBS-D versus IBS-C patients with both endpoints. The authors concluded that global binary and 50% improvement endpoints performed similarly in discriminating between non-responders and those achieving MCID, but there was a better discriminant spread for IBS-D than for IBS-C, suggesting a need for more sensitive endpoints for IBS-C.

Alternative Therapy for Metronidazole-Resistant *Clostridium difficile* Infection

C. difficile infection (CDI) has reached epidemic proportions in the United States among all age groups, particularly in the hospital setting. Toxins A and B play a major role in CDI pathogenesis, along with a recently discovered toxin—binary toxin (actin-specific ADP-ribosyltransferase toxin), which cannot be detected in stool via commercial assays. Binary toxin causes toxic megacolon and significant mortality.

Oral metronidazole has provided an effective standard therapy for CDI for over a decade. However, bacterial resistance to metronidazole has developed as a clinical challenge that warrants the investigation of salvage therapy alternatives.

Basu and associates evaluated the efficacy of the non-absorbed oral antibiotic rifaximin in cases of metronida-

zole-resistant CDI in the community. They recruited 25 patients with CDI with ages ranging from 48–65 years, 13 men and 12 women, 13 with community-acquired CDI, 12 with nursing home-acquired CDI, a mean white blood cell count of 14,000/mm³, mean creatinine of 0.9 mg/dL. All patients had mild-to-moderate CDI (5–10 bowel movements a day without sepsis). All had been exposed to antibiotics within the last 3 months. Twelve (48%) patients had been hospitalized in the last 3 months. Eighteen (72%) patients had been exposed to proton pump inhibitors in the last 3 months. All were CDI resistant to metronidazole (stools positive for toxins A and B after oral metronidazole 500 mg three times daily for 5 days).

Oral rifaximin (400 mg) was given three times daily for 14 days as salvage therapy after stopping metronidazole. Patients were followed for 56 days, and stool was tested for *C. difficile* to assess the effect of treatment. A negative PCR test was defined as favorable response to rifaximin. Patients with sepsis, abdominal distention, leukocyte count of 20,000/mm³, HIV infection, multi-organ failure, renal failure, recent (within the last 6 weeks) exposure to vancomycin or rifampicin, ventilator support, recent organ transplant, or receiving chemotherapy were excluded.

Of the patients who completed therapy (n=22), 16 (64%) eradicated the infection (negative CD PCR after 56 days). Three (12%) patients aborted therapy because of abdominal distention. In a per-protocol analysis, 72.7% of patients responded to rifaximin salvage therapy. The authors concluded that rifaximin may be considered for the treatment of mild-to-moderate metronidazole resistant CDI and that larger randomized trials are needed to support these preliminary findings.