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Presentation summaries in:

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

The 50th Annual Meeting of the European Association for the Study of the Liver

April 22-26, 2015
Vienna, Austria

Digestive Disease Week 2015

May 16-19, 2015
Washington, DC

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THE GASTRO & HEP REPORT

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FOR TREATING CHRONIC HCV GT 1

BE THE ONE WHO CAN CHANGE WHAT'S POSSIBLE.
GO TO **HARVONI.COM/HCP_J1**

HARVONI IS THE FIRST AND ONLY SINGLE-TABLET REGIMEN FOR HCV GT 1 PATIENTS BUILT ON A SOFOSBUVIR BACKBONE[1]

1

1 TABLET ONCE A DAY WITHOUT IFN OR RBV

Recommended treatment duration for HARVONI[1]:

8 weeks Can be considered in TN patients without cirrhosis who have pre-treatment HCV RNA <6 million IU/mL

12 weeks
- TN patients with or without cirrhosis
- TE patients without cirrhosis

24 weeks TE patients with cirrhosis

- Each HARVONI tablet contains 90 mg of ledipasvir and 400 mg of sofosbuvir[1]

IFN = interferon, RBV = ribavirin, TE = treatment-experienced (patients who failed treatment with either Peg-IFN alfa + RBV or an HCV protease inhibitor + Peg-IFN alfa + RBV), TN = treatment-naïve

HARVONI DELIVERED HIGH CURE (SVR) RATES IN A BROAD RANGE OF GT 1 SUBJECTS[1,a]

97% **OVERALL CURE RATE ACROSS THREE HARVONI PHASE 3 TRIALS[1-4,a]**
(n=1042/1079)

- Overall cure rates were 94%-99% in the HARVONI Phase 3 clinical trials[1]
- The HARVONI clinical trial program enrolled the most challenging subjects, regardless of GT 1a or 1b subtype, prior experience with therapy, or presence of cirrhosis[1]

[a] Sustained virologic response (SVR) was the primary endpoint and was defined as HCV RNA <25 IU/mL at 12 weeks after the cessation of treatment.[1] Achieving SVR is considered a virologic cure.[5]

Study Designs[1]: ION-3: a randomized, open-label trial in GT 1 treatment-naïve subjects (N=647) without cirrhosis. Subjects were randomized in a 1:1:1 ratio to receive HARVONI for 8 weeks, HARVONI + RBV for 8 weeks, or HARVONI for 12 weeks. **ION-1:** a randomized, open-label trial in GT 1 treatment-naïve subjects (N=865) with or without cirrhosis. Subjects were randomized in a 1:1:1:1 ratio to receive HARVONI for 12 weeks, HARVONI + RBV for 12 weeks, HARVONI for 24 weeks, or HARVONI + RBV for 24 weeks. SVR rates for all subjects enrolled in the 24-week treatment groups (N=434) were not available at the time of interim analysis. **ION-2:** a randomized, open-label trial in GT 1 treatment-experienced subjects (N=440) with or without cirrhosis. Subjects were randomized in a 1:1:1:1 ratio to receive HARVONI for 12 weeks, HARVONI + RBV for 12 weeks, HARVONI for 24 weeks, or HARVONI + RBV for 24 weeks.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Risk of Serious Symptomatic Bradycardia When Coadministered with Amiodarone:** Amiodarone is not recommended for use with HARVONI due to the risk of symptomatic bradycardia, particularly in patients also taking beta blockers or with underlying cardiac comorbidities and/or with advanced liver disease. In patients without alternative, viable treatment options, cardiac monitoring is recommended. Patients should seek immediate medical evaluation if they develop signs or symptoms of bradycardia.
- **Risk of Reduced Therapeutic Effect of HARVONI Due to P-gp Inducers:** Rifampin and St. John's wort are not recommended for use with HARVONI as they may significantly decrease ledipasvir and sofosbuvir plasma concentrations.
- **Related Products Not Recommended:** HARVONI is not recommended for use with other products containing sofosbuvir (SOVALDI®).

HARVONI WAS SAFE WITH LOW RATES OF DISCONTINUATIONS AND ADVERSE EVENTS (AEs) ACROSS CLINICAL TRIALS[1-4]

≤1% **DISCONTINUATIONS DUE TO AEs[1]**

- Adverse reactions (all grades) reported in ≥5% of subjects receiving 8, 12, or 24 weeks of treatment with HARVONI: fatigue (13%-18%), headache (11%-17%), nausea (6%-9%), diarrhea (3%-7%), and insomnia (3%-6%)[1]
- No hematologic monitoring or dose adjustments are required with HARVONI[1]

MORE THAN 110,000 PATIENTS HAVE BEEN PRESCRIBED HARVONI IN THE US[6,b]

#1 **PRESCRIBED HCV TREATMENT IN THE US[6,c]**

[b] This information is derived from IMS NPA Market Dynamics, IMS NPA Monthly data, IntegriChain DNA National, and 867 data; data reflect estimated patient starts from October 2014–April 2015.

[c] IMS Weekly NPA Market Dynamics from week-ending 10/24/14–5/15/15.

HELP YOUR PATIENTS GET STARTED ON HARVONI WITH SUPPORT PATH®

- Support Path is a suite of resources that assists with benefits investigations and prior authorizations, and identifies potential financial assistance for patients, such as the HARVONI co-pay coupon program

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

Most common (≥10%, all grades) adverse reactions were fatigue and headache.

DRUG INTERACTIONS

- In addition to rifampin and St. John's wort, coadministration of HARVONI is also not recommended with carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifapentine, and tipranavir/ritonavir. Such coadministration is expected to decrease the concentration of ledipasvir and sofosbuvir, reducing the therapeutic effect of HARVONI.
- Coadministration of HARVONI is not recommended with simeprevir due to increased concentrations of ledipasvir and simeprevir. Coadministration is also not recommended with rosuvastatin or co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate due to increased concentrations of rosuvastatin and tenofovir, respectively.

Consult the full Prescribing Information for HARVONI for more information on potentially significant drug interactions, including clinical comments.

Please see Brief Summary of full Prescribing Information on the following pages.

HARVONI®
ledipasvir/sofosbuvir
90 mg/400 mg tablets

HARVONI® (ledipasvir 90 mg and sofosbuvir 400 mg) tablets, for oral use

Brief Summary of full Prescribing Information. See full Prescribing Information. Rx Only.

INDICATIONS AND USAGE: HARVONI is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS:

Serious Symptomatic Bradycardia When Coadministered with Amiodarone: Postmarketing cases of symptomatic bradycardia, as well as fatal cardiac arrest and cases requiring pacemaker intervention, have been reported when amiodarone is coadministered with HARVONI. Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown. Coadministration of amiodarone with HARVONI is not recommended. For patients taking amiodarone who will be coadministered HARVONI and patients taking HARVONI who need to start amiodarone, who have no other alternative, viable treatment options; and due to amiodarone's long half-life for patients discontinuing amiodarone just prior to starting HARVONI: Counsel patients about the risk of serious symptomatic bradycardia; and cardiac monitoring in an in-patient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment. Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion or memory problems.

Risk of Reduced Therapeutic Effect Due to P-gp Inducers: Concomitant use may significantly decrease ledipasvir and sofosbuvir concentrations and may lead to a reduced HARVONI effect. Use of HARVONI with P-gp inducers (e.g., rifampin or St. John's wort) is not recommended.

Related Products Not Recommended: Use of HARVONI with products containing sofosbuvir (SOVALDI®) is not recommended.

ADVERSE REACTIONS:

The safety assessment of HARVONI was based on pooled data from three Phase 3 clinical trials in subjects with genotype 1 CHC with compensated liver disease (with and without cirrhosis) who received HARVONI for 8 (N=215), 12 (N=539) and 24 (N=326) weeks. Adverse events led to permanent treatment discontinuation in 0%, <1% and 1% of subjects receiving HARVONI for 8, 12 and 24 weeks, respectively.

Adverse Reactions (adverse events assessed as causally related by the investigator): The most common adverse reactions (≥10%; all grades) were fatigue and headache. Adverse reactions (all grades; majority Grade 1) observed in ≥5% of subjects by treatment duration were:

- *HARVONI for 8 weeks:* fatigue (16%); headache (11%); nausea (6%); diarrhea (4%); and insomnia (3%)
- *HARVONI for 12 weeks:* fatigue (13%); headache (14%); nausea (7%); diarrhea (3%); and insomnia (5%)
- *HARVONI for 24 weeks:* fatigue (18%); headache (17%); nausea (9%); diarrhea (7%); and insomnia (6%)

Direct comparison across trials should not be made due to differing trial designs.

Laboratory Abnormalities: ***Bilirubin Elevations:*** Bilirubin elevations of greater than 1.5x ULN were observed in 3%, <1% and 2% of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively. ***Lipase Elevations:*** Transient, asymptomatic lipase elevations of greater than 3x ULN were observed in <1%, 2% and 3% of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively. ***Creatine Kinase:*** Creatine kinase was not assessed in Phase 3 trials of HARVONI. Isolated, asymptomatic creatine kinase elevations (Grade 3 or 4) have been previously reported in subjects treated with sofosbuvir in combination with ribavirin or peginterferon/ribavirin in other clinical trials.

Postmarketing Experience

Cardiac Disorders: Serious symptomatic bradycardia has been reported in patients taking amiodarone who initiate treatment with HARVONI during post approval use of HARVONI. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

DRUG INTERACTIONS:

Ledipasvir is an inhibitor of the drug transporters P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of coadministered substrates for these transporters. Ledipasvir and sofosbuvir are substrates of P-gp and BCRP while the inactive sofosbuvir metabolite GS-331007 is not. P-gp inducers (e.g. rifampin or St. John's wort) may decrease ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect; use of HARVONI with P-gp inducers is not recommended.

Established and Potentially Significant Drug Interactions: The drug interactions described are based on studies conducted in healthy adults with either HARVONI, the components of HARVONI as individual agents, or are predicted drug interactions that may occur with HARVONI. This list includes potentially significant interactions but is not all inclusive. **An alteration in dose or regimen may be recommended for the following drugs when coadministered with HARVONI:**

- **Acid Reducing Agents:** Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease ledipasvir concentration.
  - *Antacids:* Separate HARVONI and antacid administration by 4 hours.
  - *H_2-receptor antagonists:* Doses comparable to famotidine 40 mg twice daily or lower may be administered simultaneously with or 12 hours apart from HARVONI.

Brief Summary (cont.)

  - *Proton-pump inhibitors:* Doses comparable to omeprazole 20 mg or lower can be administered simultaneously with HARVONI under fasted conditions.
- **Antiarrhythmics (amiodarone; digoxin)** *Amiodarone:* Coadministration of amiodarone with HARVONI may result in serious symptomatic bradycardia and is not recommended. Mechanism of effect is unknown. If coadministration is required, cardiac monitoring is recommended. *Digoxin:* Increased digoxin concentration. Monitor digoxin therapeutic concentration during coadministration with HARVONI.
- **Anticonvulsants (carbamazepine; phenytoin; phenobarbital; oxcarbazepine):** Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.
- **Antimycobacterials (rifabutin; rifampin; rifapentine):** Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.
- **HIV Antiretrovirals**
  - *Regimens containing tenofovir disoproxil fumarate (DF) and an HIV protease inhibitor/ritonavir (emtricitabine/tenofovir DF plus atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir):* The safety of increased tenofovir concentrations has not been established. Consider alternative HCV or antiretroviral therapy. If coadministration is necessary, monitor for tenofovir-associated adverse reactions. Refer to VIREAD or TRUVADA prescribing information for renal monitoring recommendations.
  - *Efavirenz/emtricitabine/tenofovir DF:* Monitor for tenofovir-associated adverse reactions. Refer to VIREAD, TRUVADA or ATRIPLA prescribing information for renal monitoring recommendations.
  - *Elvitegravir/cobicistat/emtricitabine/tenofovir DF:* The safety of increased tenofovir concentrations has not been established. Coadministration is not recommended.
  - *Tipranavir/ritonavir:* Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.
- **HCV Products (simeprevir):** Increased ledipasvir and simeprevir concentrations. Coadministration is not recommended.
- **Herbal Supplements (St. John's wort):** Decreased ledipasvir and sofosbuvir concentrations. Coadministration is not recommended.
- **HMG-CoA Reductase Inhibitors (rosuvastatin):** Significant increase in rosuvastatin concentrations and risk of rosuvastatin associated myopathy, including rhabdomyolysis. Coadministration is not recommended.

Drugs without Clinically Significant Interactions with HARVONI: Based on drug interaction studies conducted with HARVONI or its components, no clinically significant drug interactions have been observed or are expected when used with the following drugs individually: abacavir, atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, efavirenz, emtricitabine, lamivudine, methadone, oral contraceptives, pravastatin, raltegravir, rilpivirine, tacrolimus, tenofovir DF or verapamil.

Consult the full Prescribing Information prior to and during treatment with HARVONI for potential drug interactions; this list is not all inclusive.

USE IN SPECIFIC POPULATIONS:

Pregnancy: HARVONI is Pregnancy Category B; there are no adequate and well-controlled studies in pregnant women. HARVONI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Studies in rats have demonstrated that ledipasvir and GS-331007 are secreted in milk but had no effect on nursing pups. It is not known if HARVONI and its metabolites are secreted in human breast milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HARVONI and any potential adverse effects on the nursing child from the drug or from the underlying maternal condition.

Pediatric Use: Safety and effectiveness of HARVONI have not been established in pediatric patients.

Geriatric Use: Clinical trials of HARVONI included 117 subjects aged 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment of HARVONI is warranted in geriatric patients.

Renal Impairment: No dosage adjustment of HARVONI is required for patients with mild or moderate renal impairment. The safety and efficacy of HARVONI have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) or end stage renal disease (ESRD) requiring hemodialysis. No dosage recommendation can be given for patients with severe renal impairment or ESRD.

Hepatic Impairment: No dosage adjustment of HARVONI is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C). Safety and efficacy of HARVONI have not been established in patients with decompensated cirrhosis.

References: 1. HARVONI US full Prescribing Information. Gilead Sciences, Inc. Foster City, CA. March 2015. **2.** Afdhal N, Zeuzem S, Kwo P, et al; for the ION-1 Investigators. Ledipasvir and sofosbuvir for untreated HCV genotype 1 Infection. *N Engl J Med.* 2014;370(20):1889-1898. **3.** Kowdley KV, Gordon SC, Reddy KR, et al; for the ION-3 Investigators. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med.* 2014;370(20):1879-1888. **4.** Afdhal N, Reddy KR, Nelson DR, et al; for the ION-2 Investigators. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med.* 2014;370(16):1483-1493. **5.** US Department of Health and Human Services, Center for Drug Evaluation and Research. Draft Guidance for Industry. Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment. October 2013. **6.** Data on file, Gilead Sciences, Inc.

Presentations in Hepatology

Daclatasvir/Sofosbuvir Plus Ribavirin in Patients With Advanced Cirrhosis or Liver Transplantation

Combinations of ribavirin, pegylated interferon, and direct-acting antiviral agents have dramatically improved overall outcomes in patients with hepatitis C virus (HCV) infection. However, patients with advanced cirrhosis and those who have undergone liver transplant are still in need of oral therapies that have a shorter duration and are without drug interactions. At the 50th annual meeting of the European Association for the Study of the Liver (EASL), Fred Poordad, MD, of the University of Texas Health Science Center in San Antonio, Texas presented findings from the phase 3, open-label ALLY-1 study (Abstract LO8). The study evaluated 12 weeks of treatment with daclatasvir (60 mg once daily), sofosbuvir (400 mg once daily), and ribavirin in patients with advanced cirrhosis or recurrent HCV after liver transplant. The ribavirin dose was adjusted from 600 mg daily to 1000 mg daily based on hemoglobin levels and creatinine clearance.

The 60 advanced cirrhosis patients and 53 posttransplant patients had a median age of 59 years (range, 19-82 years), and approximately two-thirds were men. In the cirrhosis and posttransplant cohorts, respectively, 40% and 42% of patients were treatment-naive and 75% and 77% had HCV genotype 1 infection. The posttransplant patients had METAVIR fibrosis classifications of F0 to F2 (43%), F3 (25%), or F4 (30%). In the cirrhotic cohort, patients had cirrhosis of Child-Pugh class A (20%), B (53%), or C (27%), and the model for end-stage liver disease (MELD) score for the cohort ranged from 8 to 27.

After treatment with daclatasvir, sofosbuvir, and ribavirin, the rates of sustained virologic response at 12 weeks (SVR12) were 83% for the advanced cirrhosis cohort and 94% for the posttransplant cohort. Of the patients with HCV genotype 1 infection, 82% of the cirrhotic patients and 95% of posttransplant patients achieved SVR12. Among the HCV genotype 3 cohort, SVR12 rates were 83% in the 6 (10%) patients with advanced cirrhosis and 91% in the 11 (21%) patients who were posttransplant. All 4 patients with advanced cirrhosis whose treatment was interrupted for a liver transplant achieved SVR12 following posttransplant treatment, including 1 patient who received no therapy after transplant. The most common adverse events (AEs) of any grade were headache, fatigue, anemia, diarrhea, and nausea.

Longer Retreatment With Ledipasvir/Sofosbuvir Is Feasible in Patients Who Failed 8 or 12 Weeks of Treatment

Patients who fail shorter treatment with direct-acting antiviral agents may benefit from retreatment with the same drugs given for a longer time. At the EASL meeting, Eric Lawitz, MD, of the University of Texas Health Science Center in San Antonio, Texas presented efficacy and safety results from an open-label, single-arm, phase 2 study investigating retreatment with the once-daily fixed-dose combination of ledipasvir (90 mg) and sofosbuvir (400 mg) for 24 weeks in patients who had failed the same drug combination given for 8 or 12 weeks in phase 2 or 3 trials (Abstract O005).

The 41 patients had a median age of 58 years (range, 35-71 years), and 83% were men. Eighty-three percent of patients had HCV genotype 1a infection, and the mean HCV RNA level was 6.2 $\log_{10}$ IU/mL (range, 4.5-7.4 $\log_{10}$ IU/mL). Of the 19 (46%) patients with cirrhosis, 79% had baseline NS5A resistance-associated variants (RAVs). Prior treatment duration was 8 or 12 weeks for 30 and 11 patients, respectively, and NS5A RAVs were present in 63% and 100% of these patients, respectively.

After 4 or 8 weeks of treatment, HCV RNA was undetectable in 95% and 100% of patients, respectively. One virologic breakthrough occurred at week 16, and several patients experienced relapse after cessation of treatment. The SVR4 and SVR12 rates were 73% and 71%, respectively. SVR12 rates for noncirrhotic vs cirrhotic patients were similar (68% vs 74%; Figure 1). However, a greater difference in SVR12 rates emerged for prior treatment duration of 8 weeks vs 12 weeks (80% vs 46%, respectively).

Baseline NS5A RAVs were associated with a SVR12 rate of 60% vs a rate of 100% in the absence of these variants. Moreover, baseline NS5A RAVs were more common in patients whose prior treatment lasted 12 weeks. Patients with 0, 1, or at least 2 baseline NS5A RAVs yielded SVR12 rates of 100%, 69%, and 50%, respectively, and specific baseline RAVs were associated with SVR12 rates ranging from 33% for baseline Y93H/N mutations (n=6) to 100% for baseline Q30R (n=4) or M28T (n=1). The majority of AEs were of mild or moderate severity. Two serious AEs occurred and were considered unrelated to study treatment. No treatment discontinuations were attributed to an AE, and no deaths occurred during the study.

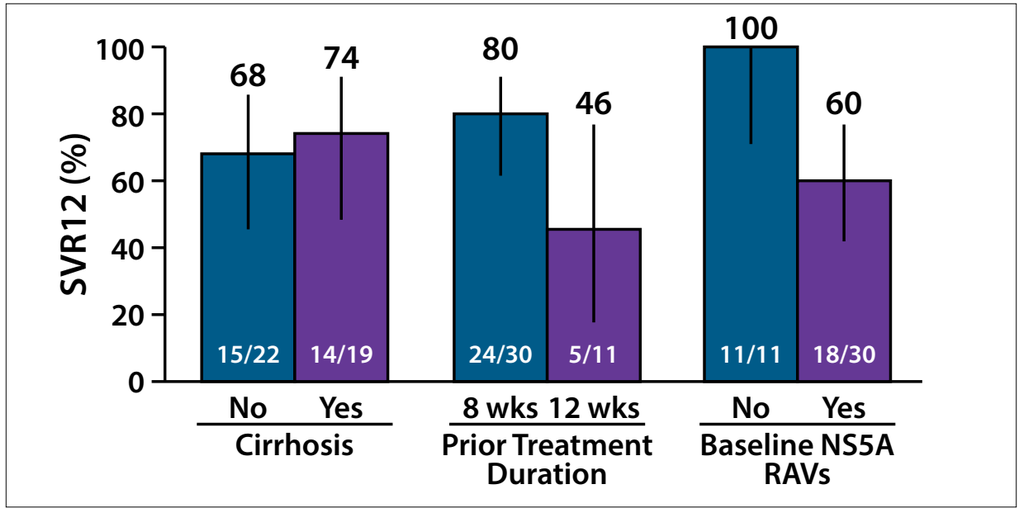

Figure 1. SVR12 in a trial evaluating retreatment of patients who failed 8 or 12 weeks of ledipasvir/sofosbuvir-based regimens with an additional course of ledipasvir/sofosbuvir.

RAV, resistance-associated variants; SVR12, sustained virologic response at week 12.

Adapted from Lawitz E et al. Retreatment of patients who failed 8 or 12 weeks of ledipasvir/sofosbuvir-based regimens with ledipasvir/sofosbuvir for 24 weeks [EASL abstract O005]. *J Hepatol*. 2015;62(1)(suppl).

Sofosbuvir/Ledipasvir and Ribavirin Treatment Demonstrates Efficacy in Patients Who Have Hepatitis C Virus Infection and Advanced Liver Disease

Effective and safe treatments are needed for patients with chronic HCV infection and advanced cirrhosis, particularly those with decompensated cirrhosis. At the EASL meeting, Michael Manns, MD, of the Hannover Medical School in Hannover, Germany presented preliminary safety and efficacy findings from the international SOLAR-2 (GS-US-337-0124) study, which investigated a single-tablet, 2-drug regimen of sofosbuvir (400 mg) and ledipasvir (90 mg) plus ribavirin taken for 12 or 24 weeks (Abstract G02). SOLAR-2 enrolled treatment-naive or -experienced patients with HCV genotype 1 or 4 infection at 34 sites in 12 countries. All patients had either decompensated liver disease or recurrent HCV infection following a liver transplant. The study included 168 posttransplant patients who had no cirrhosis, based on METAVIR stage F0 to F3, or had compensated cirrhosis, based on Child-Turcotte-Pugh class A. The study also included 160 patients with decompensated cirrhosis, based on Child-Turcotte-Pugh class B or C, of whom 53 were posttransplant. Patients in each cohort were randomized 1:1 to 12 or 24 weeks of treatment. Patients with a Child-Turcotte-Pugh score of 13 or higher were excluded.

The median age of the entire study population was approximately 59 years (range, 27-79 years), approximately three-fourths were men, and approximately 11% of patients had HCV genotype 4 infection. For the cohort of F0 to F3 and Child-Turcotte-Pugh class A patients, the SVR12 rates were 95% and 98% for 12 vs 24 weeks of treatment, respectively. For the patients with decompensated cirrhosis, SVR12 rates were 85% and 88% for 12 vs 24 weeks of treatment, respectively. For the patients with HCV genotype 1 infection, 12 vs 24 weeks of treatment yielded SVR12 rates of 96% vs 98% for the noncirrhotic or compensated cirrhosis patients and 88% vs 89% for patients with decompensated cirrhosis. The analysis included only 36 patients with HCV genotype 4 infection, thus precluding meaningful conclusions for this group. In the patients with decompensated cirrhosis, virologic response was accompanied by improvements in MELD and Child-Turcotte-Pugh scores and by improved levels of bilirubin and albumin. Treatment-related serious AEs were reported in 0% to 5% of patients in each of the 4 arms, and no deaths were considered treatment-related.

Favorable Rates of Sustained Virologic Response at 12 Weeks Observed After 8 Weeks of Treatment With Grazoprevir, Elbasvir, and Sofosbuvir

A shortened duration of treatment is desirable for patients with HCV infection. At the EASL meeting, Fred Poordad, MD, of the University of Texas Health Science Center in San Antonio, Texas presented results from the open-label,

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Table 1. Treatment Arms in the C-SWIFT Trial of Grazoprevir, Elbasvir, and Sofosbuvir in Patients With HCV Genotype 1 or 3 Infection

Cirrhosis Status	Treatment Duration	n
Noncirrhotic	4 weeks	31
Noncirrhotic	6 weeks	30
Cirrhotic	6 weeks	20
Cirrhotic	8 weeks	21
Noncirrhotic	8 weeks	15
Noncirrhotic	12 weeks	14
Cirrhotic	12 weeks	12

HCV, hepatitis C virus.

Data from Poordad F et al. C-SWIFT: grazoprevir/elbasvir + sofosbuvir in cirrhotic and noncirrhotic, treatment-naive patients with hepatitis C virus genotype 1 infection for durations of 4, 6 or 8 weeks and genotype 3 infection for durations of 8 or 12 weeks [EASL abstract O006]. *J Hepatol.* 2015;62(1)(suppl).

phase 2 C-SWIFT trial, which investigated a shortened duration of treatment with a daily fixed-dose tablet of grazoprevir (100 mg) and elbasvir (50 mg), plus daily sofosbuvir (400 mg) in patients with HCV genotype 1 or 3 infection, with or without cirrhosis (Abstract O006).

The 102 patients with HCV genotype 1 infection received 4, 6, or 8 weeks of treatment, with treatment durations of 4 or 6 weeks for noncirrhotic patients and 6 or 8 weeks for cirrhotic patients (Table 1). The 41 patients with HCV genotype 3 infection received 8 or 12 weeks of treatment, with treatment durations of 8 or 12 weeks for noncirrhotic patients and 12 weeks for cirrhotic patients. The median age across the 7 treatment arms ranged from 42 to 57 years, with a median age of approximately 52 years for the entire study group. Cirrhosis was reported in 37% of the patients.

For HCV genotype 1 patients, SVR12 rates for noncirrhotic patients after 4 vs 6 weeks of treatment were 33% vs 87%. For cirrhotic patients after 6 vs 8 weeks of treatment, SVR12 rates were 80% vs 94%. For HCV genotype 3 patients, SVR12 rates for noncirrhotic patients after 8 vs 12 weeks of treatment were 93% vs 100%, and the cirrhotic patients achieved a SVR12 rate of 91% after 12 weeks of treatment. All virologic failures were due to relapse, and the majority of relapsing patients had either wild-type HCV infection at relapse or RAVs that were present at baseline. The novel drug combination was generally well tolerated. The most common AEs were headache, fatigue, and nausea. One cirrhotic patient discontinued treatment due to an AE, and 2 cirrhotic patients experienced a serious AE.

Systematic Review and Meta-Analysis of Hepatitis B Virus Reactivation in Patients Receiving Chemotherapy for Solid Tumors

For patients receiving chemotherapy for solid tumors, the risk of reactivation of hepatitis B virus (HBV) has not been established. At the Digestive Disease Week (DDW) 2015 meeting, Sonali Paul, MD, of the Tufts Medical Center in Boston, Massachusetts presented results of a systematic review and meta-analysis investigating HBV reactivation rates with or without prophylaxis in patients with solid malignancies and in chronic vs resolved HBV infection (Abstract 730).

The analysis included studies through March 31, 2015 available from MEDLINE, PubMed, Web of Science, Cochrane Central Register of Controlled Trials, TOXNET, and Scopus. The researchers included 22 studies of chronic HBV infection, representing 1578 patients, and 3 studies of resolved HBV infection, representing 322 patients. Twenty-four studies were observational, 1 was a randomized controlled trial, and 21 studies were from Asian countries. Patients had a median age of 47 years (range, 20-80 years) and had cancer of the breast (n=844), head and neck (n=335), gastrointestinal tract (n=274), or another area (n=125).

In patients with chronic HBV infection, the rate of reactivation without antiviral prophylaxis was 22% (95% CI, 17%-28%), with substantial heterogeneity among the included studies (Cochrane I^2, 81%). The rate of reactivation in patients given antiviral prophylaxis was 4.6% (95% CI, 2.2%-7.9%), and heterogeneity was lower (I^2, 61%). Forest plot analysis demonstrated that prophylaxis reduced the risk of reinfection in HBV patients receiving chemotherapy (odds ratio [OR], 0.14; 95% CI, 0.08-0.24; I^2, 5%). The risk of reinfection ranged from 14% to 24% based on tumor type and from 3.3% to 32% based on type of chemotherapy. Prophylaxis decreased the rates of hepatitis (OR, 0.19; 95% CI, 0.11-0.33) and delayed chemotherapy (OR, 0.13; 95% CI, 0.05-0.37). None of the patients with resolved HBV infection received prophylaxis; their rate of reinfection was 2.2% (95% CI, 0%-8.6%), and heterogeneity was low (I^2, 15%).

Infection-Related Acute-on-Chronic Liver Failure as a Predictor of Mortality in Patients With Cirrhosis

In patients with chronic cirrhosis, infection reduces survival. Infection-related acute-on-chronic liver failure (I-ACLF) status is defined as 2 or more extrahepatic organ failures and is used to classify patients with cirrhosis and sepsis to enable more effective intervention. At the DDW meeting, Jacqueline O'Leary, MD, of the Baylor University Medical Center in Dallas, Texas presented results of a study whose aim was to validate the ability of I-ACLF status to predict 30-day mortality in cirrhotic patients with infection (Abstract 591). The multicenter study examined data from prospectively enrolled patients in the North American Consortium for the Study of End-Stage Liver Disease database of tertiary care hepatology centers. The study included 336 infected patients and 449 uninfected patients who were hospitalized with a complication of cirrhosis. Assessments were performed for organ failure based on the presence of shock, grade 3/4 hepatic encephalopathy, need for dialysis, or need for mechanical ventilation.

Patients had a mean age of 57 years, 64% were men, and 43% had alcohol-induced cirrhosis. Mean baseline levels of serum creatinine, sodium, MELD scores, and Child-Pugh scores were higher in the infected patients, while mean baseline serum albumin levels and blood pressure were lower. Thirty-day survival decreased with an increasing number of organ failures, regardless of the presence of infection. Any single organ failure was correlated with a lower rate of survival for infected patients compared with uninfected patients. Based on multivariable modeling, the area under the curve for mortality was 0.81 for the entire group, 0.82 for infected patients, and 0.73 for uninfected patients. I-ACLF was the strongest predictor of 30-day survival (OR, 0.10; 95% CI, 0.06-0.22) for infected as well as uninfected patients after controlling for baseline MELD score, white blood cell count, serum albumin level, and infection status.

Obeticholic Acid for the Treatment of Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) is a chronic, autoimmune, cholestatic liver disease that destroys the bile ducts and can lead to liver transplant or death. Disease progression is marked by increasing levels of plasma alkaline phosphatase and bilirubin. Obeticholic acid is a modified bile acid and agonist of the farnesoid X receptor that has demonstrated efficacy and tolerability in patients with PBC. Its mechanism of action differs from that of ursodeoxycholic acid (UDCA), which yields an inadequate response or is intolerable in as many as half of patients but is the only drug currently approved to treat PBC. At the DDW meeting, Kris Kowdley, MD, of the Swedish Medical Center in Seattle, Washington presented findings of an integrated analysis of results from 2 placebo-controlled phase 2 studies (747-201 and 747-202) and the phase 3 POISE study that evaluated obeticholic acid with or without UDCA in patients with PBC (Abstract 657).

The analysis included a total of 335 patients who had an inadequate response to or were unable to tolerate UDCA. The POISE study had a composite endpoint of alkaline phosphatase level of less than 1.67 times the upper limit of normal, with a minimum 15% reduction and a normal bilirubin level. Significantly more patients achieved the composite endpoint after treatment with obeticholic acid compared with placebo or UDCA monotherapy in each of the 3 studies (P<.05 for each). In the pooled analysis, 8% of the 124 placebo-treated patients and 45% of the 306 patients treated with obeticholic acid achieved the composite endpoint (P<.0001). Obeticholic acid treatment in the 3 studies was associated with significantly improved levels of alkaline phosphatase, bilirubin, gamma-glutamyl transpeptidase, alanine transaminase, and aspartate transaminase from baseline to the end of treatment. Treatment was generally well tolerated. The most common AE was pruritus, which occurred in 63% of patients treated with obeticholic acid (10 mg daily).

Hepatology

Presentations in IBD

Withdrawal of Anti–Tumor Necrosis Factor α Therapy in Patients Who Have Inflammatory Bowel Disease

In the United Kingdom, reassessment of inflammatory bowel disease (IBD) activity after 12 months of therapy is mandated by The National Institute for Health and Care Excellence and the Scottish Medicines Consortium. The guidelines mandate discontinuation of therapy in most patients who demonstrate clinical remission and mucosal healing. At the DDW meeting, Nicholas Kennedy, MD, of the Western General Hospital in Edinburgh, United Kingdom presented results of a retrospective study of relapse rates in IBD patients following withdrawal of anti–tumor necrosis factor α (anti-TNFα) therapy and results of a systematic review of related literature (Abstract 288).

Included patients had a confirmed diagnosis of IBD and at least 12 months of prior anti-TNFα therapy. The trial's primary endpoint was moderate-to-severe relapse at 12 months. The study included 146 patients with Crohn's disease (CD) and 20 with ulcerative colitis (UC) or unclassified IBD. Approximately 85% of patients were being treated with infliximab, and the remainder were being treated with adalimumab. The median time on anti-TNFα therapy was 28 months (range, 14-45 months), and the median follow-up was approximately 2 years. All patients were in clinical remission at the time of therapy cessation, and 62.5% had normal levels of C-reactive protein (CRP), fecal calprotectin, and other laboratory parameters. Complete mucosal healing was observed in 89 of the 102 patients, with endoscopy performed prior to treatment cessation.

Relapse rates at 1 and 2 years were 36% and 56% for patients with CD and 42% and 47% for patients with UC or unspecified IBD. Of the patients who relapsed within 12 months, 24 patients were given systemic corticosteroids, 7 were admitted to the hospital, and 2 underwent resectional surgery. For the CD patients, multivariable analysis modeled without fecal calprotectin identified the risk factors of age at diagnosis of less than 22 years (hazard ratio [HR], 2.29; 95% CI, 1.35-3.88) and white blood cell count greater than 5.25×10^9/L (HR, 2.06; 95% CI, 1.11-3.80 × 10^9/L). For the 42 CD patients with available fecal calprotectin data, multivariable analysis identified levels of fecal calprotectin greater than 50 µg/g as a risk factor (HR, 3.04; 95% CI, 1.26-7.37). A systematic review and meta-analysis yielded relapse rates of 39% for patients with CD (HR, 0.39; 95% CI, 0.35-0.43) and 37% for patients with UC (HR, 0.37; 95% CI, 0.28-0.46).

Relapse After Withdrawal of Anti–Tumor Necrosis Factor α Therapy in Patients With Crohn's Disease

Patients in remission from CD could benefit from cessation of anti-TNFα therapy; however, as many as 50% of patients relapse. At the DDW meeting, Martin Bortlik, MD, of the Charles University in Prague, Czech Republic presented results from a study designed to elucidate risk factors for relapse, including the importance of deep remission (Abstract 283).

The prospective, observational study included consecutive patients from a single center who discontinued anti-TNFα therapy at the time of corticosteroid-free, clinical and endoscopic remission. Deep remission was defined as the presence of endoscopic and clinical remission, with a calprotectin level of less than 150 mg/kg and a CRP level of 5 mg/L or lower. Relapse was defined as clinical worsening confirmed either by imaging, laboratory parameters, or the new onset of perianal disease.

The 61 enrolled patients had a median age of 31 years (range, 15-65 years), and 59% were women. The median duration of anti-TNFα therapy at the time of discontinuation was 23 months (range, 4-73 months), and 77% of patients continued immunosuppressive therapy after stopping anti-TNFα treatment. Median follow-up after cessation of anti-TNFα therapy was 28 months (range, 7-47 months).

Thirty-two (53%) patients relapsed, with a median time to relapse of 8 months (range, 1-25 months). Remission was maintained for 6, 12, or 24 months in 82%, 59%, and 51% of patients, respectively. The relapse rates in 27 patients with deep remission vs 23 patients without deep remission were similar (*P*=.84). In multivariate analysis, patients with colonic disease were less likely to relapse compared with patients who had ileal or ileocolonic disease at 1 year (OR, 0.15; 95% CI, 0.03-0.72; *P*=.02) and at the end of follow-up (HR, 0.30; 95% CI, 0.10-0.87; *P*=.03). Factors that did not influence the risk of relapse included the type of anti-TNFα therapy, the type of immunosuppressive therapy, corticosteroid use, and levels of calprotectin or CRP. Sixteen of the 32 patients were re-treated with anti-TNFα agents, and 87.5% exhibited a response. Of the remaining patients, 4 underwent surgery and 12 received a different type of treatment for their CD.

Infliximab Vs Placebo For Patients With Crohn's Disease Following Ileocolonic Resection

At the DDW meeting, Miguel Regueiro, MD, of the University of Pittsburgh Medical Center in Pittsburgh, Pennsylvania presented results of the PREVENT trial, which examined the efficacy of infliximab vs placebo for preventing clinical recurrence in patients with CD following intestinal resection with ileocolonic anastomosis (Abstract 749). The primary endpoint of the randomized, double-blind, placebo-controlled trial was the prevention of clinical recurrence of CD by week 76 of postsurgical treatment.

Key patient inclusion criteria included documented diagnosis of CD, CD activity index of less than 200, and ileocolonic resection within 45 days prior to enrollment. Clinical recurrence was defined as a CD activity index of greater than 200 with a greater-than-70-point increase from baseline, endoscopic recurrence, and a negative stool test result for *C difficile* infection; development of a new fistula or redraining of an existing fistula or abscess also constituted clinical recurrence. Two hundred ninety-seven patients were randomized to receive infliximab (5 mg/kg) or placebo treatment. Patients had a median CD activity index of 106. Medications in use at baseline included corticosteroids (4.7%), immunomodulators (17.5%), and aminosalicylates (18.5%), and 22.6% of patients had a history of anti-TNFα use. Patients in the 2 treatment arms had similar risk factors for recurrence.

After 76 weeks of treatment, the placebo and infliximab treatment arms showed clinical recurrence rates of 20.0% and 12.9%, respectively (*P*=.097). The time to clinical recurrence was not significantly different between the 2 treatment arms (*P*=.141). For the secondary endpoint of endoscopic recurrence, with data handling rules applied, the infliximab and placebo arms demonstrated recurrence in 60.6% and 30.6% of patients, respectively (*P*<.001).

In the placebo vs infliximab arms, 8.9% vs 29.4% of patients discontinued study treatment due to an AE, and at least 1 infusion reaction was reported in 8.2% vs 19.4% of patients. Noted study limitations included a clinical recurrence rate that was lower than expected, enrollment of a low-risk study population, and subjectivity of the CD activity index.

Serum Neutrophil Gelatinase-Associated Lipocalin and Matrix Metalloproteinase 9 as a Marker of Mucosal Healing in Patients With Crohn's Disease

Examination of serum markers of mucosal healing could provide a less costly alternative to endoscopy for patients with CD. At the DDW meeting, Magali de Bruyn, PhD, of the Rega Institute for Medical Research in Leuven, Belgium described results of a study investigating serum levels of neutrophil gelatinase-associated lipocalin and matrix metalloproteinase 9 (NGAL-MMP-9) as a surrogate marker for mucosal healing in patients with CD (Abstract Su1219).

The study included 108 patients with active CD and 43 healthy controls. All participants received an infliximab infusion, and NGAL-MMP-9 levels were determined by sandwich enzyme-linked immunosorbent assay (ELISA) before the first infliximab infusion and up to 5 years after. Endoscopic healing was defined as the complete absence of ulcerations; partial healing was defined as significant endoscopic improvement with ulcerations present. Histologic healing was defined as the absence of epithelial damage.

Of the 108 patients with active CD, complete or partial endoscopic healing was observed in 38 (35%) and 34 (31%) patients, respectively, and no endoscopic healing was observed in 36 (33%) patients. At baseline, the median level of NGAL-MMP-9 was 77.6 ng/mL (interquartile range [IQR], 36.9-141.0 ng/mL) in patients with CD vs 25.5 ng/mL (IQR, 17.8-42.8) in healthy controls (*P*<.001). After infliximab treatment, NGAL-MMP-9 levels decreased significantly relative to baseline in the 72 patients with healing (69.0 ng/mL; IQR, 32.6-135.5 ng/mL vs 35.2 ng/mL; IQR, 9.4-56.1 ng/mL; *P*<.001). Serum levels of the marker also decreased in the 36 patients with CD who did not exhibit endoscopic healing, from 100.9 ng/mL (IQR, 43.4-152.6 ng/mL) at baseline to 43.8 ng/mL (IQR, 27.0-96.8 ng/mL) after treatment (*P*<.002). However, the decrease was significantly more profound in patients with complete healing (*P*=.020). Levels of NGAL-MMP-9 correlated with the level of neutrophils (*P*<.001) and CRP (*P*<.001), endoscopic activity (*P*<.001), and histologic activity (*P*<.001).

Based on receiver operating characteristic analysis, a serum NGAL-MMP-9 cutoff level of 26.4 ng/mL corresponded with complete endoscopic healing and histologic healing. Sensitivity and specificity were 58% and 85%, respectively, for endoscopic healing and 63% and 84%, respectively, for histologic healing. The results compared favorably to those associated with CRP, for which a cutoff of 5 mg/mL showed specificities of 58% and 52% for endoscopic healing or histologic healing, respectively.

Statins Provide a Protective Effect Against New-Onset Inflammatory Bowel Disease

Exposure to medication has been identified as a possible trigger for the onset of IBD. At the DDW meeting, Ryan Ungaro, MD, of the Icahn School of Medicine at Mount Sinai in New York, New York described results of a study that investigated the relationship between exposure to specific classes of medication and the risk of new-onset IBD (Abstract 7).

The matched case-control study identified patients from a national medical claims and pharmacy database. The study included adult patients with international classification of diseases (ICD)-9 codes of 555.x for CD and 556.X for UC between January 2008 and December 2012. Using propensity scoring, each IBD patient had up to 10 matched controls based on age, sex, race, and state. Controls had no ICD-9 codes for CD, UC, or IBD-associated diseases and no prescriptions for IBD medications. New-onset IBD was defined as having at least 3 separate CD or UC ICD-9 codes and at least 1 year with no IBD-related codes.

Consistent with prior publications, the analysis found that the new onset of IBD was more likely after exposure to trichomonacides (OR, 1.89; 95% CI, 1.83-1.95), other antibiotics (OR, 2.45; 95% CI, 2.18-2.76), injectable estrogens (OR, 1.66; 95% CI, 1.09-2.51), and transdermal estrogens (OR, 1.28; 95% CI, 1.18-1.39), as well as after exposure to aminoglycosides and quinolones. However, combinations of progesterone plus estrogen showed a protective effect (OR, 0.86; 95% CI, 0.83-0.90), as did oral contraceptives without estrogen (OR, 0.88; 95% CI, 0.78-0.98). Notably, the analysis identified HMG-CoA reductase inhibitors, including simvastatin, atorvastatin, and pravastatin, as having a protective effect against the new onset of IBD (OR, 0.68; 95% CI, 0.66-0.69). The protective effect was observed for CD (OR, 0.63; 95% CI, 0.61-0.65) and for UC (OR, 0.72; 95% CI, 0.69-0.74).

Recurrent *Clostridium difficile* Infection in Patients With Inflammatory Bowel Disease

Clostridium difficile infection (CDI) is more common in IBD patients than in the general population. At the DDW meeting, Roshan Razik, MD, of Mount Sinai Hospital in Toronto, Ontario described results from the RECIDIVISM study, which examined the incidence of CDI and recurrent infection in IBD (Abstract 594).

The investigators retrospectively reviewed records from the Division of Infectious Diseases CDI Database between 2010 and 2013 to identify IBD patients who had recurrent CDI (2 or more incidents of CDI), 1 CDI incident, and non-IBD patients. The review identified 54 (11%) patients with CD, 56 (11%) patients with UC, and 393 (78%) patients with no bowel disease. The entire study population had a mean age of 58.8 years, and 61.4% of the subjects were women.

Table 2. Recurrent *Clostridium difficile* Infection in Inflammatory Bowel Disease

Risk Factor	OR (95% CI)	*P* Value
Nonileal Crohn's disease	2.59 (1.66-4.05)	<.001
Recent antibiotic therapy	2.60 (1.55-4.35)	<.001
5-ASA use	3.06 (1.78-5.29)	<.001
Corticosteroid use	2.94 (1.70-5.10)	<.001
Biologic therapy	2.50 (1.45-4.31)	.001
Recent hospitalization	2.62 (1.64-4.20)	<.001
No previous bowel resections	1.72 (1.09-2.72)	.020

5-ASA, 5-aminosalicylic acid; OR, odds ratio.

Adapted from Razik R et al. Recurrence of *Clostridium difficile* infection in patients with inflammatory bowel disease—the RECIDIVISM study [DDW abstract 594]. *Gastroenterology*. 2015;148(4)(suppl).

Compared with the non-IBD population, IBD patients with CDI had a lower age (39 years vs 64 years; *P*<.001), used more corticosteroids (39.1% vs 12.0%; *P*<.001) and more immunosuppressive medications (42.7% vs 13.2%; *P*<.001), and were more likely to have had a prior bowel resection (28.2% vs 11.5%; *P*<.001). Recurrent CDI was noted in 32% of IBD patients vs 24% of non-IBD patients (*P*<.01), and the time to recurrence was longer for the IBD vs non-IBD patients (213.7 months vs 124.0 months; *P*<.001). IBD patients were more likely to undergo colectomy due to infection with *C difficile* (6.4% vs 0.3%; *P*<.001). CDI-attributable mortality occurred in 12.2% of the non-IBD population vs 0% of the IBD population (*P*<.001).

Based on multivariate analysis, statistically significant predictors of recurrent CDI in the IBD population included recent hospitalization and recent use of antibiotics, 5-aminosalicylic acid, corticosteroids, biologic therapy, or immunosuppressants (*P*≤.001 for each). CDI was more likely to recur in patients with nonileal CD (*P*<.001), and IBD patients without a prior bowel resection were more likely to experience CDI recurrence (*P*=.020; Table 2).

Zinc Intake and the Risk of Inflammatory Bowel Disease

Zinc has effects on autophagy, the innate and adaptive immune response and maintenance of the intestinal barrier. Based on results in cell culture, the role of zinc in metalloproteinases and other enzymes, and the association between zinc deficiency and more severe colitis, dietary zinc may play a role in the development of IBD. At the DDW meeting, Ashwin Ananthakrishnan, MD, of Massachusetts General Hospital in Boston, Massachusetts described results of a prospective study that investigated the association between zinc intake and the risk of CD and UC within 2 cohorts of women (Abstract 5). Dietary zinc levels were determined by means of the validated semiquantitative food frequency questionnaire, which was administered every 4 years, and included food sources of zinc as well as zinc supplements and multivitamins.

The study population included 170,809 women from the Nurses Health Studies I and II, representing 3,317,550 person-years of follow-up. The investigators identified 269 incident cases of CD, yielding an incidence of 8 per 100,000 person-years, and 338 cases of UC, yielding an incidence of 10 per 100,000 person-years. Zinc intake ranged from 9 mg daily in the lowest quintile to 33 mg daily in the highest quintile. Increased zinc intake was associated with a reduced risk of CD. Compared with the lowest quintile of zinc intake, HRs for quintiles 2, 3, 4, and 5 (representing increasing amounts of zinc intake), respectively, were 0.92 (95% CI, 0.65-1.29), 0.60 (95% CI, 0.40-0.89), 0.57 (0.38-0.86), and 0.74 (95% CI, 0.50-1.10). In contrast, no significant relationships were observed between zinc intake and risk of UC.

Compared with patients with daily zinc intake of less than 8 mg daily, a reduced risk of CD was observed for those with daily zinc intake of 8 to 16 mg daily (HR, 0.69; 95% CI, 0.44-1.08) and for those with daily zinc intake of greater than 16 mg daily (HR, 0.52; 95% CI, 0.32-0.86). Results remained robust after adjusting for dietary vitamin C, phytates, or calcium.

Presentations in Endoscopy

Outcomes of a 5-Year Series of Peroral Endoscopic Myotomy

Peroral endoscopic myotomy (POEM) is an endoscopic procedure for the treatment of motility disorders of the esophagus. The procedure is related to natural orifice transluminal endoscopic surgery and was developed to deliver the long-term benefits of surgical myotomy by using flexible endoscopes, thus avoiding the costs and complications associated with surgery. At the DDW meeting, Stavros Stavropoulos, MD, of Winthrop University Hospital in Mineola, New York described results from a 5-year, prospective series of POEM performed in patients with achalasia at a single tertiary care center (Abstract 181).

The 204 patients in the series had a mean age of 53 years (range, 10-93 years), including 16 patients over 80 years. Prior achalasia treatment included pneumatic balloon dilation (17%), suboptimal balloon dilation (22%), botulinum toxin (20%), and Heller myotomy (15%). Seventy-three percent of patients had stage I or II achalasia, and 10% of patients had stage III achalasia. Of the 17% of patients with stage IV disease, 34 of 35 patients had sigmoid disease, with an esophageal diameter ranging from 6 to 13.5 cm.

After POEM treatment, the Eckardt score decreased from a mean of 7.7 (range, 4-12) at baseline to a mean of 0.2 (range, 0-3) at the 3-month assessment ($P<.0001$). Clinical success, defined as an Eckardt score of 3 or less, was observed in 97% of patients at the 3-, 6-, and 12-month follow-up assessments. Lower esophageal sphincter pressure decreased from a baseline mean of 42.9 mm Hg (range, 5.4-111 mm Hg) to a mean of 18.3 mm Hg (range, 0-50 mm Hg) at the 3-month follow-up assessment ($P<.0001$).

Of the 70 patients who were tested for barium emptying at 5 minutes, all exhibited greater than 50% emptying, and 40 (57%) patients exhibited 100% emptying. The mean hospital stay was 1.8 days (range, 1-6 days). Six POEM failures occurred in the series, and 5 of these patients were successfully treated with salvage therapy. No deaths occurred. Minor AEs were observed in 7 (3%) patients, and 2 (1%) patients required readmission within 30 days of POEM. Objective gastroesophageal reflux disease (GERD) assessment at 3 months showed 39 (40%) of 98 patients with reflux esophagitis and 36 (37%) of 97 patients with a positive pH test result.

Prophylactic Clip Placement After Snare Polypectomy

Delayed gastrointestinal bleeding is a known complication of snare polypectomy. Some reports suggest that gastrointestinal bleeding can be prevented by the use of prophylactic clips. At the DDW meeting, Tarun Rai, MD, of the Kansas City Veterans Administration Medical Center in Kansas City, Missouri presented results from a systematic review and meta-analysis that investigated the role of prophylactic clip placement after snare polypectomy to prevent delayed gastrointestinal bleeding (Abstract 329).

Two independent reviewers conducted a search of PubMed, EMBASE, the Cochrane Central Register of Controlled Trials and Database of Systematic Reviews, and recent abstracts from major conference proceedings, using the search terms *polyp*, *bleeding*, *colonoscopy*, and *clips*. Randomized and nonrandomized studies comparing prophylactic clip placement with no clip placement were included, and pooled data were generated for delayed postpolypectomy bleeding, overall complications, and perforation rates.

The analysis included 2 randomized and 6 case-control studies comprising 12,108 patients and 8354 polypectomies. In polypectomies with vs without prophylactic clip placement, postpolypectomy bleeding was observed in 1.1% vs 0.82% of patients, respectively. Analysis of pooled data demonstrated no significant differences between the 2 groups in terms of rates of delayed bleeding (OR, 1.14; 95% CI, 0.31-4.17; $P=.84$; I^2, 79%), overall complications (OR, 0.64; 95% CI, 0.28-1.46; $P=.29$; I^2, 45%), or perforation (OR, 1.41; 95% CI, 0.25-8.09; $P=.70$; I^2, 0%).

Risk Factors for Bleeding After Polypectomy in Patients on Antithrombotic Agents

Few studies have investigated the relationship between the use of anticoagulants and bleeding after polypectomy, and there is no consensus regarding optimal timing for reintroducing anticoagulants after endoscopy. At the DDW meeting, David Lin, MD, of the Veterans Affairs Palo Alto Health Care System in Palo Alto, California presented results of a systematic review of bleeding complications following polypectomy performed by 24 endoscopists at 2 tertiary care centers between January 2004 and June 2012 (Abstract 331). The study's aim was to investigate the inci-

dence and risk factors of bleeding after polypectomy for patients on antithrombotic therapies.

The study included consecutive patients undergoing elective colonoscopy who were on antithrombotic agents and experienced hematochezia within 1 month after polypectomy. Three matched control cases were selected for each bleeding patient based on antithrombotic agent, polypectomy technique, procedure date, and study site. The overall incidence of postpolypectomy bleeding was 1.2% (95% CI, 0.91%-1.54%). The highest incidence of bleeding was observed in the 87 patients on heparin (14.9%; 95% CI, 8.20%-24.4%), followed by aspirin (0.92%; 95% CI, 0.64%-1.26%; n=3933), clopidogrel (0.84%; 95% CI, 0.27%-2.00%; n=595), and warfarin only (0.66%; 95% CI, 0.18%-1.69%; n=604).

The 59 patients with postpolypectomy bleeding and the matched controls had similar baseline characteristics, with a median age of approximately 65 years and similar rates of hypertension, heart disease, and kidney disease. Patients who experienced bleeding after polypectomy were more likely to have a polyp of 2 cm or larger (41% vs 10%; *P*<.001), and the mean size of the largest polyp was greater in patients who experienced bleeding after polypectomy (13.9 ± 14.6 vs 7.3 ± 4.3; *P*<.001).

The study identified several characteristics that were more common among patients who bled after polypectomy vs those who did not, such as restarting medication within 1 week of polypectomy (75% vs 34%; OR, 4.5; 95% CI, 2.2-9.4; *P*<.001), having at least 1 polyp measuring 2 cm or greater (41% vs 10%; OR, 5.9; 95% CI, 2.7-12.9; *P*<.001), or having multiple large polyps (20% vs 8%; OR, 2.9; 95% CI, 1.1-7.3; *P*=.001). Cautery in the right colon was also more common in patients who bled after polypectomy (76% vs 55%; OR, 2.6; 95% CI, 1.3-5.5; *P*=.004). The rate of prophylactic clip placement was similar between the 2 cohorts (*P*=.32).

Chromoendoscopy for Detecting Dysplasia in Patients With Long-Standing Ulcerative Colitis

Patients with UC have an increased risk of colorectal cancer compared with the general population. In comparison to white-light endoscopy, chromoendoscopy can provide images with improved resolution and better contrast through the concomitant use of dyes, such as indigo carmine and methylene blue. At the DDW meeting, Venkat Subramanian, MD, of the Saint James University Hospital in Leeds, United Kingdom presented results of a randomized, parallel-group study evaluating rates of dysplasia detection using high-definition white-light endoscopy (HDWLE) vs high-definition chromoendoscopy (HDCE) in patients with long-standing UC (Abstract 446).

High-definition equipment was used for all procedures. A 0.2% indigo carmine spray was applied on withdrawal using a dye spray catheter, and targeted and quadrantic random biopsies were taken from each colonic segment in all study participants. Included patients had UC of more than 8 years' duration extending proximal to the splenic flexure and requiring surveillance colonoscopy. The study randomized 53 patients to HDWLE and 50 patients to HDCE. Patients in both arms had a median age of approximately 55 years and a mean duration of disease of approximately 22 years. Both arms were generally well matched in terms of family history of colorectal cancer, smoking status, and medication use.

The number of patients with dysplasia detected was significantly higher in the HDCE arm vs the HDWLE arm (22% vs 9.4%; *P*=.04). Six low-grade lesions were detected with HDWLE, whereas HDCE detected 1 high-grade and 13 low-grade lesions. The mean number of dysplastic lesions detected per patient was also higher with HDCE (0.26 ± 0.6 vs 0.12 ± 0.4; *P*=.04). Mean withdrawal time was significantly higher in the HDCE arm than in the HDWLE arm (21.2 ± 5.8 minutes vs 13.6 ± 3.3 minutes; *P*<.001). No dysplastic lesions were detected in any of the random biopsies.

Endoscopic Mucosal Resection for the Removal of Large and Flat Lesions of the Colon

Large and flat colonic lesions are at increased risks of bleeding, perforation, and incomplete removal with traditional snare resection. Although patients with these types of lesions are usually referred to surgery, advanced endoscopic techniques could provide a less invasive alternative. At the DDW meeting, Gottumukkala Raju, MD, of the MD Anderson Cancer Center in Houston, Texas presented results of a study that investigated endoscopic mucosal resection of large and flat lesions in patients referred to a single center between 2009 and 2012 (Abstract 1062).

The study included 205 patients with lesions of presumed benign pathology. Patients had a mean age of 64 years (range, 29-88 years), and approximately half of the patients were men. The majority of lesions (61%) were located in the right colon. Patients had lesions that were less than 10 mm (25%), 10 to 20 mm (28%), or greater than 20 mm (47%).

Of the 205 patients, 8 (3.8%) had an optical diagnosis of cancer, underwent biopsy confirmation, and were referred to surgery; 40 (19.3%) patients could not undergo the endoscopic procedure for various reasons, including 16 patients in whom access to the lesion was difficult; and 159 (76.8%) patients experienced a successful endoscopic procedure. Complications occurred in 6 (3.7%) patients and included delayed bleeding in 5 patients, of whom 3 required hospitalization, and 1 patient with a perforation that was successfully closed without surgery.

Surveillance colonoscopy was performed in 139 patients at 3 to 6 months after endoscopic mucosal resection and in 60 patients at 18 months after resection. In 6 patients, residual tumor was observed and removed by repeating the endoscopic procedure. Precancerous lesions observed during surveillance included adenomas (2.78%) and serrated polyps (0.84%).

A Novel, Edible Preparation for Effective Bowel Cleansing for Colonoscopy

Proper preparation for colonoscopy is essential for accurate results, yet as many as 25% of colonoscopy preparations are inadequate. Many patients fail to complete cleansing due to poor taste and the large volume of fluid that must be ingested. At the DDW meeting, Campbell Levy, MD, of the Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire presented findings from a study that evaluated a novel, nutritionally balanced, low-residue diet incorporating a purgative agent that was developed to replace fasting and liquid cleansing (Abstract Su1525). The study's primary aim was to determine the feasibility of the novel bowel cleansing preparation in patients undergoing colonoscopy.

Adults scheduled for colonoscopy for colorectal cancer screening or surveillance of polyps at a single center were eligible. Meals, snacks, and drinks blended with polyethylene glycol 3350, sorbitol, and ascorbic acid were provided. The protocol specified stopping the study after enrollment of 30 patients or after 8 of 10 patients, enrolled in groups of 5, achieved a global colon preparation assessment of good or excellent.

The study was halted after all 10 of the first 10 enrolled patients had successful colon cleansing, including 1 patient with a global assessment of excellent and the remainder with an assessment of good. The 10 patients had a median age of 61 years (range, 46-73 years). Indications included screening for colorectal cancer (70%) and adenoma surveillance (30%). Eight patients completed 100% of the preparation, and 2 patients completed 95% of the preparation.

All patients gave the experimental preparation an overall tolerability rating of 1 on a 5-point scale, indicating no problems with the preparation. All 10 patients also indicated a willingness to take the preparation again for a subsequent procedure. No significant changes in electrolyte or creatinine levels were observed, and no AEs were reported.

Endoscopy

Presentations in IBS

Validation of a Serologic Test for Diarrhea-Predominant Irritable Bowel Syndrome

Due to a lack of disease-specific biomarkers, diarrhea-predominant irritable bowel syndrome (IBS-D) is diagnosed by excluding other diagnoses, such as IBD and celiac disease. Animal models injected with *Campylobacter jejuni* produce host antibodies against cytolethal distending toxin B (CdtB) that can crossreact with vinculin in the host gut, inducing symptoms similar to those of IBS, and the crossreactivity has been replicated in human colon tissue samples. At the DDW meeting, Mark Pimentel, MD, of the Cedars-Sinai Medical Center in Los Angeles, California presented results of a large study that evaluated antibodies to CdtB and vinculin as biomarkers for IBS-D (Abstract 311).

The study recruited 2375 IBS-D patients who met the Rome III criteria from the multicenter TARGET 3 trial. The study also recruited 142 patients with IBD, 121 patients with celiac disease, and 43 healthy subjects. Plasma levels of anti-CdtB and antivinculin antibodies were determined by ELISA to evaluate differences in antibody levels among the study cohorts.

Levels of anti-CdtB antibodies and antivinculin antibodies were significantly higher in IBS patients compared with all other cohorts in aggregate and compared with each non-IBS cohort (P<.00001 for all comparisons). A key goal of the study was to optimize the ability of the antibody test to distinguish IBS-D from IBD. An optical density cutpoint of 2.80 was identified for the anti-CdtB ELISA, which conferred a specificity of 91.6%, sensitivity of 43.7%, and likelihood ratio of 5.2. For antivinculin, the optimal optical density cutpoint of 1.68 was identified, with a specificity of 83.8%, sensitivity of 32.6%, and likelihood ratio of 2.0.

Successful Retreatment With Rifaximin for Symptomatic Diarrhea-Predominant Irritable Bowel Syndrome

Abdominal pain, bloating, and urgency are common symptoms of patients with IBS-D. At the DDW meeting, William Chey, MD, of the University of Michigan in Ann Arbor, Michigan presented results of a multiphase, randomized, controlled trial that assessed the efficacy of rifaximin retreatment in patients who responded to an initial course of the same antibiotic (Abstract 313).

The study enrolled patients with IBS-D who met Rome III criteria and had mean severity scores of at least 3 for abdominal pain (on a scale of 0-10) and at least 3 for bloating (on a scale of 0-6). Patients also had at least 2 stools that were type 6 or 7 (ie, loose or watery) on the Bristol Stool Scale during the 7-day baseline evaluation. After this evaluation, eligible patients received open-label rifaximin (550 mg) 3 times daily.

Patients who experienced symptom recurrence within 18 weeks were randomized to the double-blind portion of the study, in which patients received treatment with rifaximin (550 mg) or placebo 3 times daily; patients received the same treatment during two 2-week periods separated by 10 weeks without treatment. Abdominal pain, bloating, stool consistency, and urgency were assessed by daily questionnaires. Efficacy was defined as patients with a positive response during at least 2 of 4 weeks following treatment, and recurrence was defined as a loss of response for at least 3 of 4 weeks following treatment. The primary endpoint was the proportion of patients experiencing a decrease of at least 30% in mean abdominal pain and a concomitant decrease of at least 50% in the number of days per week with stool consistency matching Bristol Stool Scale type 6 or 7.

For the first repeat treatment, 308 patients were randomized to placebo and 328 patients were randomized to rifaximin; for the second repeat treatment, 283 were randomized to placebo and 295 were randomized to rifaximin. Prior to repeat treatment, the 2 arms were well balanced in terms of demographics and IBS-D symptoms. The trial met its primary endpoint, with rifaximin yielding a significantly higher proportion of composite responders than placebo after the first retreatment (35% vs 25%; P=.005). Significant improvements were also observed for rifaximin compared with placebo for specific IBS-D symptoms after the first retreatment period, including abdominal pain, stool consistency, bloating, and urgency (P<.05 for each). Rifaximin also yielded a greater proportion of composite responders after the second retreatment (37% vs 29%; P=.0375). Rifaximin treatment was generally well tolerated.

Tenapanor for the Treatment of Constipation-Predominant Irritable Bowel Syndrome

Tenapanor is an investigational small molecule that reduces sodium and phosphate uptake from the gut. In a

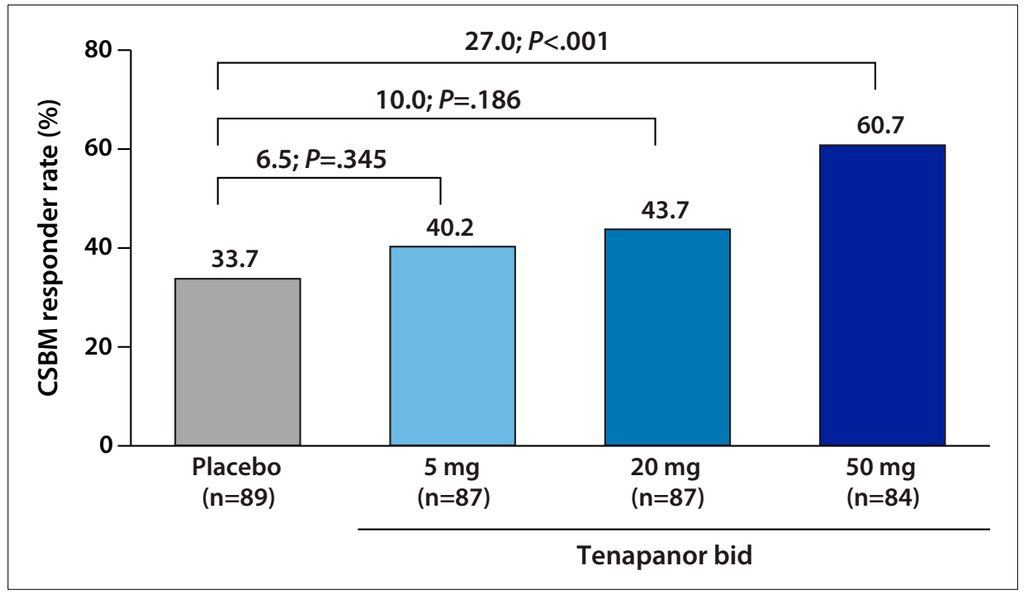

Figure 2. The proportion of patients with an increase of at least 1 complete spontaneous bowel movement (CSBM) per week from baseline for at least 6 of the 12 treatment weeks.

Adapted from Chey W et al. Efficacy and safety of tenapanor in patients with constipation-predominant irritable bowel syndrome: a 12-week, double-blind, placebo-controlled, randomized phase 2b trial [DDW abstract 1020]. *Gastroenterology.* 2015;148(4)(suppl).

phase 2a trial, tenapanor improved symptoms of constipation-predominant IBS (IBS-C). At the DDW meeting, William Chey, MD, of the University of Michigan in Ann Arbor, Michigan presented results of a double-blind, randomized, placebo-controlled phase 2b trial that evaluated the efficacy and safety of tenapanor for the treatment of IBS-C (Abstract 1020).

Enrolled patients were adults up to 75 years of age who had IBS-C, as defined by Rome III criteria, and active disease during the screening period. Patients were randomized to receive 12 weeks of twice-daily treatment with tenapanor, dosed at 5 mg, 20 mg, or 50 mg, or placebo. The primary endpoint was the complete spontaneous bowel movement (CSBM) responder rate, defined as the proportion of patients with an increase of at least 1 CSBM per week from baseline for at least 6 of the 12 treatment weeks.

The 356 randomized patients had a mean age of 45.7 years, and 87% were women. The 4 treatment arms were well balanced for baseline disease characteristics assessed during screening. After treatment, the CSBM responder rates for placebo vs 5 mg, 20 mg, or 50 mg of tenapanor were 33.7%, 40.2%, 43.7%, and 60.7%, respectively, and reached significance for the highest dose of tenapanor vs placebo (P<.001; Figure 2). Overall responders experienced a decrease in abdominal pain of at least 30% and an increase of at least 1 CSBM per week for at least 6 of the 12 treatment weeks. Placebo vs 5 mg, 20 mg, or 50 mg of tenapanor yielded overall responder rates of 23.6%, 25.3%, 33.3%, and 50.0%, respectively, with the final result achieving significance relative to placebo (P<.001). Compared with placebo, tenapanor (50 mg twice daily) also significantly improved stool consistency (1.0 vs 2.2; P<.001) and yielded a greater proportion of patients with an abdominal pain response (65.5% vs 48.3%; P=.026).

Most AEs were mild to moderate in severity. Three serious AEs occurred, none of which were considered treatment-related. The most common AE was diarrhea, occurring in 11.2% of patients receiving tenapanor at the highest dose. Tenapanor concentration was below the lower limit of quantification in more than 97% of serum samples, and the highest concentration measured was 1.03 ng/mL.

Characterization of Irritable Bowel Syndrome Symptoms After Ingestion of Fructose or Inulin

Fermentable carbohydrates can induce IBS symptoms; however, few studies have shown a direct association between IBS symptoms and ingestion of specific carbohydrates. At the DDW meeting, Giles Major, MD, of the University of Nottingham in Nottingham, United Kingdom presented results of a double-blind crossover study that examined the relationship between ingestion of fructose or inulin and the development of clinically important symptoms (Abstract 246).

Enrolled patients were adults 65 years or younger with IBS, as defined by Rome III criteria, and bloating. On each of 3 study days, patients received a drink that included either 40 g of fructose, 40 g of inulin, or 40 g of glucose. All drinks were flavored with lime and looked identical, and study days were scheduled at least 1 week apart to avoid crossover. The primary endpoint was the composite score for the symptoms of flatulence, bloating, pain, and diarrhea, with each symptom scored on a scale of 0 to 3. An increase of at least 3 points in the composite score relative to baseline was considered symptomatic. Other outcomes included breath hydrogen, small bowel water content, and colonic volume and gas, with the latter 2 assessed by magnetic resonance imaging.

Twenty-nine patients, of whom 22 were women, completed all 3 study treatments. The median age was 34 years (range, 25-48.5 years). Symptom intensity was greater after ingestion of fructose or inulin compared with glucose (P<.05 for both). In the responding patients, the time to peak symptom intensity was approximately 1 hour after fructose ingestion vs approximately 4 hours with inulin (P<.005). Median breath hydrogen levels increased from 1 ppm (range, 0.5-3 ppm) after glucose ingestion to 18 ppm (range, 5-50 ppm; P<.005) after fructose ingestion and to 66 ppm (range, 31.5-125.5 ppm; P<.005) after inulin ingestion.

Median colonic volume increased from 56 mL ± 59 mL with glucose to 142 mL ± 140 mL (P<.05) with fructose and to 265 mL ± 191 mL with inulin (P<.005). Fructose induced a greater increase in small bowel water content compared with glucose (P<.005), and both test carbohydrates caused a greater increase in colonic gas compared with glucose (P<.05 for fructose; P<.005 for inulin). In symptomatic patients, peak IBS symptoms were most strongly correlated with small bowel water content after fructose ingestion (R=.51) and with colonic gas after inulin ingestion (R=.57).

Efficacy of Lubiprostone in Constipation-Predominant Irritable Bowel Syndrome Patients With Different Baseline Pain Scores

Lubiprostone is a selective chloride channel activator that has demonstrated efficacy in treating symptoms of IBS-C. At the DDW meeting, Lin Chang, MD, of the David Geffen School of Medicine at the University of California, Los Angeles in Los Angeles, California presented results of a post hoc analysis of data from 2 trials in IBS-C evaluating the efficacy of lubiprostone and the impact of baseline abdominal pain on response rates (Abstract Mo1262).

The post hoc analyses included data from 2 double-blind, randomized, placebo-controlled, phase 3 trials of lubiprostone in patients with IBS-C. Response rates were determined by a scale ranging from 0, indicating no symptoms, to 4, indicating very severe symptoms. Eligible patients had a baseline pain score of at least 1.36. Responders were defined as having a mean pain reduction of at least 30% compared with baseline and an increase of at least 1 SBM per week for 6 of 12 treatment weeks. The efficacy of lubiprostone on abdominal pain alone was also evaluated.

In study 1, composite response rates were 25.5% (39 of 153 patients) with lubiprostone vs 13.0% (10 of 77 patients) with placebo (P=.0338). In study 2, composite response rates were 27.2% (37 of 136 patients) with lubiprostone and 17.4% (15 of 86 patients) with placebo (P=.3275). Using a baseline pain score of at least 1.36, the pooled data showed that lubiprostone significantly improved response rates (26.3% vs 15.3%; P=.0079). The improvement in response rate with lubiprostone was observed for patients with a baseline pain score of at least 1.5 (P=.0180) or at least 2.0 (P=.0069). No significance was observed for baseline pain scores of at least 2.5 or at least 3.0, but data from a limited number of patients were available for these analyses.

Presentations in GERD

5-Year Results of a Magnetic Device for the Treatment of Gastroesophageal Reflux Disease

In March 2012, the US Food and Drug Administration approved the LINX magnetic device, which is surgically implanted at the lower esophageal sphincter for the treatment of GERD. The device is constructed of linked, expandable magnetic beads and mechanically restores antireflux competency to the esophagus. At the DDW meeting, Robert Ganz, MD, of the University of Minnesota in Minneapolis, Minnesota presented final results of a 5-year, prospective, multicenter study evaluating the efficacy and safety of the device (Abstract 688).

The study enrolled 100 patients at 13 centers in the United States and 1 center in the Netherlands. Included patients were age 18 to 85 years and had at least 6 months of typical heartburn, with or without regurgitation. Patients were on proton pump inhibitors (PPIs) and were partially responsive to daily PPI therapy. Patients had pathologic acid exposure and no esophageal motility disorders. Clinical efficacy and tolerability were assessed by comparing each patient's symptoms and AEs before vs after implantation of the device.

Five-year data were available for 85 patients. GERD health-related quality-of-life (HRQL) scores improved over 5 years, with median scores decreasing from 27 without PPI therapy to 11 with PPI therapy at baseline and to 4 after magnetic sphincter augmentation without PPI therapy. Outcomes that improved at 5 years vs baseline with patients not taking PPI therapy included dissatisfaction related to reflux (from 95% to 7.1%), moderate or severe heartburn (from 89% to 11.9%), and moderate or severe regurgitation (from 57% to 1.2%). The proportion of patients taking daily PPIs decreased from 100% at baseline to 15.3% at 5 years, and the proportion of patients taking double doses of PPIs decreased from 36% to 2%. The incidence of esophagitis decreased from 40% at baseline to 16% at 5 years.

The device exhibited acceptable safety, with no mucosal breaks related to the device, no device erosion or migration, and no operative AEs. The most important AE was dysphagia, which was typically mild, and affected 68% after implantation vs 7% after 5 years; however, daily, bothersome dysphagia was reported by 5% of patients at baseline and 6% of patients at 5 years. Device removal was performed in 7 patients due to dysphagia (n=4), ongoing reflux (n=2), or vomiting (n=1).

Cost-Effectiveness of Corticosteroid Therapy Vs the 6-Food Elimination Diet for the Treatment of Eosinophilic Esophagitis

First-line treatment for eosinophilic esophagitis can consist of swallowed topical corticosteroids or the 6-food elimination diet, which involves removing milk, egg, wheat, soy, nuts, and seafood from a patient's diet. Both approaches involve significant costs: corticosteroids are inherently expensive, and the 6-food elimination diet requires multiple sequential endoscopies to assess response and identify triggers. At the DDW meeting, Cary Cotton, MD, of the University of North Carolina at Chapel Hill in Chapel Hill, North Carolina presented results of a study examining the cost-effectiveness of these 2 treatment options (Abstract 4).

The authors performed a decision analysis invoking a Markov model for the choice between corticosteroid therapy and the 6-food elimination diet as first-line therapy. Patients receiving corticosteroid therapy accumulated costs for 1 postdiagnosis endoscopy to assess response to treatment and 2 months of an induction dose of corticosteroids comprising either fluticasone (1760 µg daily) or budesonide (2 mg daily), plus ongoing treatment at half of the induction dose for responders. Patients with a response to dietary therapy underwent 7 endoscopies. The cohort was limited to 10,000 patients, and crossover to the alternative treatment was allowed.

In the base case analysis, at 1 year after initiating treatment, patients in the corticosteroid treatment arm had accumulated $4765.17 in costs vs $3035.66 for the patients with dietary restriction, and both arms had accumulated 0.98 quality-adjusted life-years (QALYs). The reduced cost and similar accumulation of QALYs continued through 5 years, at which point the accumulated costs were $13,231.43 for initial corticosteroid therapy, with 4.70 QALYs, and $8817.59 for initial diet therapy, with 4.71 QALYs. In the vast majority of probabilistic sensitivity analyses, the 6-food elimination diet was cost-effective over corticosteroid therapy. The study was limited by a 5-year time horizon, reflecting the available data.

GERD

Risk Factors for Progression to Esophageal Adenocarcinoma for Patients With Barrett Esophagus and Low-Grade Dysplasia

Patients with Barrett esophagus and low-grade dysplasia are at risk of progression to esophageal adenocarcinoma. However, estimates of progression rates are limited by heterogeneity in pathologic assessments. At the DDW meeting, Rajesh Krishnamoorthi, MD, of the Mayo Clinic in Rochester, Minnesota presented results of a study that examined the rates and predictors of progression in patients with Barrett esophagus and low-grade dysplasia (Abstract Sa1067).

Included patients had Barrett esophagus with a histologic diagnosis of low-grade dysplasia and were part of a large, prospective registry in a tertiary care center. Progressors were defined as patients who developed high-grade dysplasia or esophageal adenocarcinoma more than 12 months after the index date. The study assessed several risk factors relating to patient demographics, endoscopic and histologic findings, and use of medications, with univariate and multivariate analyses performed to identify predictors of progression.

The mean age of the 337 included patients was 63 years, and 84% were men. Mean follow-up was 7 years. Twenty-one (6.2%) patients progressed to high-grade dysplasia/esophageal adenocarcinoma, and the annual incidence of progression to high-grade dysplasia/esophageal adenocarcinoma was 0.8%. Based on univariate analysis, factors that increased the risk of progression included increasing Barrett esophagus segment length (HR, 1.140; 95% CI, 1.004-1.294; *P*=.0434) and the presence of nodules (HR, 5.54; 95% CI, 1.61-19.03; *P*=.0065). Longer follow-up duration after the diagnosis of low-grade dysplasia, which likely reflected the persistence of low-grade dysplasia, was associated with a reduced risk of progression (HR, 0.780; 95% CI, 0.680-0.894; *P*=.0003).

Multivariate analysis confirmed increased duration of follow-up (HR, 0.763; 95% CI, 0.661-0.880; *P*=.0002) and increasing Barrett esophagus segment length (HR, 1.211; 95% CI, 1.049-1.397; *P*=.0088) as risk factors for progression. In addition, younger age at diagnosis of low-grade dysplasia (HR, 0.954; 95% CI, 0.919-0.989; *P*=.0110) was associated with the risk of progression. The results suggest that patients with a longer Barrett esophagus segment length and younger age when diagnosed with low-grade dysplasia may be candidates for intensive surveillance or endoscopic therapy.

Use of a Sleep-Positioning Device to Reduce Symptoms of Nocturnal Gastroesophageal Reflux Disease

Nocturnal acid reflux can damage the esophagus and has been associated with the development of esophagitis. The MedCline sleep-positioning device was designed to improve upper body elevation and lateral positioning of the left side of the body, allowing patients to sleep in an inclined position. At the DDW meeting, Sanath Allampati, MD, of the Cleveland Clinic in Cleveland, Ohio presented results from a prospective trial that examined the ability of the MedCline sleep-positioning device to improve nocturnal symptoms of GERD (Abstract Mo1137).

Enrolled patients were on antisecretory medications with continued frequent moderate-to-severe nocturnal heartburn and regurgitation. Upon enrollment and at the end of the study, patients completed the GERD-HRQL Questionnaire and the Nocturnal GERD Symptom Severity and Impact Questionnaire (N-GSSIQ), which queries nocturnal GERD symptoms, morning impact of GERD, and concerns about nocturnal GERD. Patients were instructed to continue taking antisecretory medication and to sleep on the sleep-positioning device for at least 6 hours each night for 2 weeks.

Of the 25 patients, 24 were taking PPIs and 1 patient was taking a histamine-2 receptor antagonist. At the end of the 2-week study period, mean N-GSSIQ scores had significantly improved relative to baseline (54.6 vs 17.0; *P*<.001). Improvement occurred in all 3 subsections of the questionnaire, including nocturnal GERD (33.6 vs 9.3; *P*<.001), morning impact of nocturnal GERD (6.2 vs 2.2; *P*<.001), and concern about nocturnal GERD (14.7 vs 5.5; *P*<.001). Improvement from baseline also occurred in the 16 patients who completed the GERD-HRQL Questionnaire (28.4 vs 16.3; *P*<.001). No AEs were reported.

Bone Structure and Metabolism in Users of Long-Term Proton Pump Inhibitor Therapy

Based on observational studies that have demonstrated an association between the use of PPIs and bone fractures resulting from osteoporosis, PPI prescribing information carries a black-box warning regarding possible increased risk of bone fracture with their use. At the DDW meeting, Laura Targownik, MD, of the University of Manitoba in Winnipeg, Manitoba presented results of a study that used quantitative 3-dimensional computed tomography (CT) to investigate bone structure in patients who had taken long-term PPI medication (Abstract 781).

The study initially identified all persons residing in Manitoba, Canada over the age of 50 years who had either taken PPIs continuously for at least 5 years or had not taken any PPIs during the previous 5 years. A random sample of patients from these groups was contacted for participation in the study. Bone mineral density of the hip

Table 3. Markers of Bone Metabolism

	PPI Users (n=52)	Non-PPI Users (n=52)
Calcium (mmol/L)	2.35 ± 0.07	2.32 ± 0.09
Magnesium (mmol/L)	0.86 ± 0.06	0.88 ± 0.06
Phosphate (mmol/L)	1.02 ± 0.20	1.02 ± 0.16
25-hydroxy vitamin D (nmol/L)	76.8 ± 22	74 ± 25.3
Bone-specific alkaline phosphatase (ug/L)	14.3 ± 5.5	13.4 ± 3.5
Osteocalcin (ng/L)	22.6 ± 8.8	23.1 ± 8
C-telopeptide (pg/mL)	379 ± 148	387 ± 154
[a]Gastrin (ng/L)	106 ± 70	27.5 ± 19.6

[a]*P*<.001.

PPI, proton pump inhibitor.

Adapted from Targownik L et al. Comparing bone structure and bone metabolism between long-term proton pump inhibitor users and non-users [DDW abstract 781]. *Gastroenterology*. 2015;148(4)(suppl).

and spine was assessed by standard 2-dimensional, dual-energy X-ray absorptiometry, and the left hip was scanned by 3-dimensional CT. Blood was collected to assess levels of bone metabolism markers.

The analysis included 52 patients with long-term PPI use and 52 controls. The 2 groups demonstrated similar demographic characteristics. The median age was 65 years, and approximately half of the patients were women. The mean T-score for the total hip bone, assessed by dual-energy X-ray absorptiometry, was -0.32 ± 1.01 for the PPI users and -0.29 ± 1.16 for the control group. T-scores for the femoral neck, intertrochanteric area, and L1-L4 vertebrae were similar for both cohorts. A T-score of less than -1 for the entire hip bone was observed in 30 (58%) of the PPI users and 29 (56%) of the control patients.

The 2 groups also showed similar levels of bone metabolism markers in the blood, although gastrin levels differed significantly between the PPI users vs nonusers (106 ± 70 ng/L vs 27.5 ± 19.6 ng/L; *P*<.001; Table 3). In the PPI users vs the controls, 3-dimensional CT yielded similar levels of bone mineral density for the total hip bone (341 ± 59 mg/cm^3 vs 333 ± 59 mg/cm^3), the cortical bone (1090 ± 95 mg/cm^3 vs 1075 ± 107 mg/cm^3), and trabecular bone (119 ± 22 mg/cm^3 vs 112 ± 19 mg/cm^3), and measures of bone strength were similar for both groups.

Sex Differences in Proton Pump Inhibitor Dose Requirements for the Treatment of Gastroesophageal Reflux Disease

Women on long-term PPI therapy have significantly higher fasting and postprandial gastrin levels than men (Helgadottir et al. *Dig Liv Dis*. 2014;46[2]:125-130). Therefore, men might require higher PPI doses than women for managing symptoms of GERD. At the DDW meeting, Holmfridur Helgadottir, MD, of the National University Hospital of Iceland in Reykjavik, Iceland presented results of a study investigating the relationship between PPI dose and gastrin levels in men vs women (Abstract Mo1153).

The study enrolled 49 women and 51 men with erosive esophagitis. Patients had a median age of 59 years. PPI therapy included omeprazole (n=28), rabeprazole (n=41), and esomeprazole (n=38). All patients received omeprazole for 2 months during the study and were randomized to continue at the same dose or to take half of their previous dose by weight for 2 months. Forty-nine patients were randomized to continue with the same PPI dose, 34 were randomized to reduce the daily PPI dose from 20 mg to 10 mg, and 17 were randomized to reduce the daily dose from 40 mg to 20 mg. Failures were defined as patients who left the study and resumed their prior medication. Two patients were excluded from the analysis.

Female patients had significantly higher baseline gastrin levels than male patients (76 pg/mL vs 50 pg/mL; *P*=.017). The failure rate was 2 times higher in the dose reduction group vs the control group (24% vs 13%). From baseline to the end of study treatment, median gastrin levels decreased from 71 pg/mL to 53 pg/mL (*P*=.002) for the entire dose reduction group and increased slightly in the control group (52 pg/mL vs 56 pg/mL; *P*=.04). Among the patients randomized to dose reduction, 3 (12%) of the female patients failed to complete the 2 months of reduced dose therapy vs 9 (36%) of the male patients (*P*=.09). Of the women taking 20 mg or 40 mg at baseline, 13% and 11%, respectively, failed to successfully complete 2 months of therapy at the lower dose. Median age, median baseline gastrin levels, proportion with *Helicobacter pylori* infection, and body mass index were similar for the patients with successful vs unsuccessful dose reduction.

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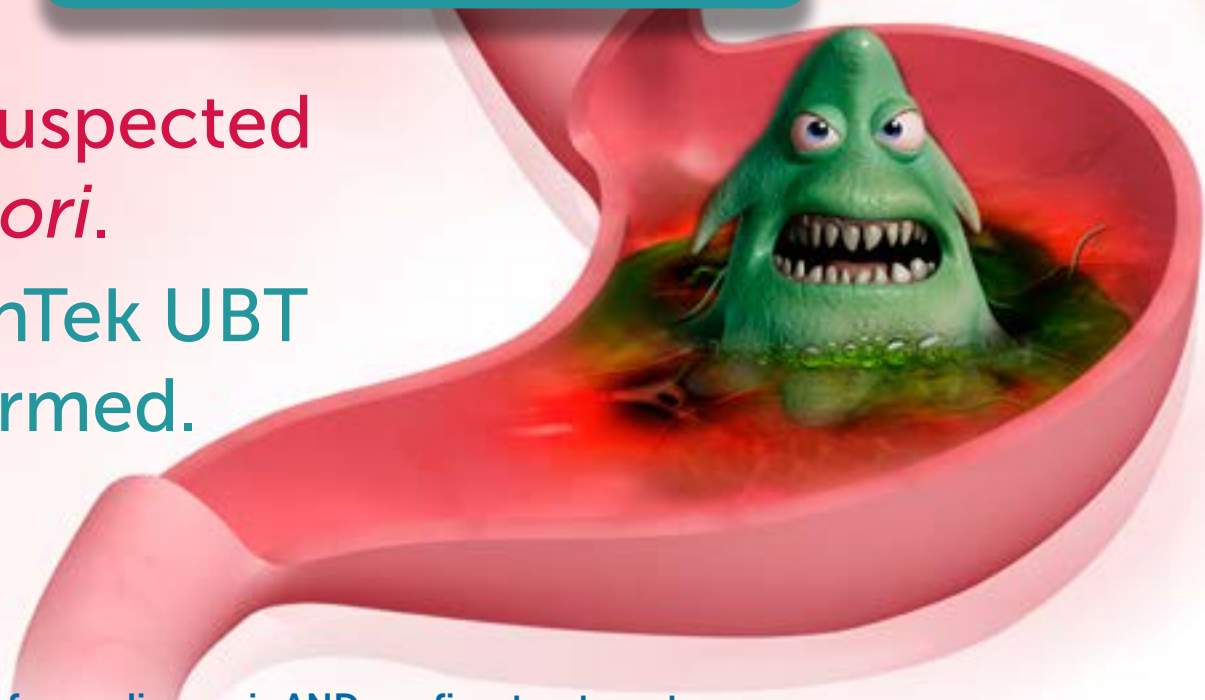

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