

## THE GASTRO & HEP REPORT

### Presentation summaries in:

8 GERD

10 IBS

15 Hepatology

18 IBD

21 Endoscopy

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

- The 46th Annual Meeting of the European Association for the Study of the Liver

March 30–April 3, 2011

Berlin, Germany

- Digestive Disease Week 2011

May 7–10, 2011

Chicago, Illinois

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# Presentations in GERD

## Dietary Fat Intake Is Associated with Development of Esophageal Adenocarcinoma

Barrett esophagus (BE) is a premalignant condition that can lead to esophageal adenocarcinoma (EAC), which is the most rapidly increasing cancer in the United States. The pathophysiology of the progression from gastroesophageal reflux disease (GERD) to BE, and potentially to EAC, is still being investigated. Evidence suggests that diet may play a role in the development of both BE and EAC.

In a prospective cohort study presented at Digestive Disease Week (DDW) 2011, Yates and colleagues evaluated the association between dietary fat and the development of BE and EAC in 23,658 healthy men and women recruited between 1993 and 1997. The European Prospective Investigation of Cancer study used nutritional data from 7-day food diaries collected at study entry. The diaries included information on food types consumed, brands, quantities, frequency of intake, and cooking methods. Participants were followed and assessed for the development of BE or EAC, and diagnoses were confirmed by medical record review.

Overall, 80 participants had a new diagnosis of BE during the follow-up period; 80% of these individuals were male, and the median age was 69.4 years (range, 41–84 years). Another 58 participants were diagnosed with EAC; 84% of these patients were male, and their median age was 73 years (range, 52–86 years). After adjusting for age, gender, smoking, body mass index (BMI), and total energy intake, the investigators found a nonsignificant trend toward higher incidence of EAC with increased fat intake. Compared to individuals in the lowest quintile of fat intake, those in the highest quintile were greater than 3 times more likely to develop EAC (hazard ratio [HR], 3.77; 95% confidence interval [CI], 0.83–17.03;  $P=.085$ ), for an overall trend HR of 1.54 (95% CI, 1.08–2.19). There was also an association between saturated fat intake and EAC (trend HR, 1.35; 95% CI, 1.01–1.79) but not between total polyunsaturated fat intake and EAC (trend HR, 1.11; 95% CI, 0.87–1.42). No associations were noted between fat intake and the risk of BE. However, the investigators suggested that the role of fat intake in the development of BE should be studied further, as the individuals with BE in this cohort were diagnosed after developing symptoms and undergoing gastroscopy.

## Longer Duration of Reflux Monitoring Improves Diagnostic Consistency

How the duration of reflux monitoring affects clinical parameters has not been fully determined. Therefore, in a

study presented at DDW 2011, Fox and colleagues prospectively evaluated the effects of monitoring duration on the measurements acquired and the consistency of GERD diagnoses. The study enrolled 163 consecutive patients with mostly typical reflux symptoms (heartburn and regurgitation) who underwent prolonged, 4-day, wireless pH recording. The researchers determined measurement variability, diagnostic consistency of acid exposure time, symptom index, and symptom association probability using a cross-validation procedure. To compare outcomes among study durations, each 4-day record was divided into 1-day sections and reassembled into all possible subsets.

The duration of pH monitoring had no significant effect on acid exposure time or symptom index. However, as the duration of pH monitoring increased, the symptom association probability also increased. Consistency in the GERD diagnosis increased with study duration for all parameters studied—including acid exposure time, symptom index, and symptom association probability—regardless of the threshold used.

## Nonsteroidal Anti-Inflammatory Drugs and Statins Are Effective as Chemoprevention in Patients with Barrett Esophagus

At DDW 2011, Kastelein and colleagues presented results of a multicenter, prospective, cohort study evaluating the effects of nonsteroidal anti-inflammatory drugs (NSAIDs) and statins on the risk of developing EAC in patients with BE. The study included 570 patients with BE of at least 2 cm; 72% of patients were male, and patients' mean age was 55 years.

The investigators gathered information on medication use based on a patient questionnaire regarding use of over-the-counter medications and patient interviews (which were checked against multiple pharmacy records). Patients were followed for a median of 7.9 years (range, 5.9–11.8 years); patients were excluded from the analysis if they developed high-grade dysplasia (HGD) or EAC in the first 9 months after entry into the study.

A total of 38 patients developed HGD or EAC during the follow-up period. Nearly all patients (99%) used a proton pump inhibitor (PPI) during this time. In addition, a majority of patients (70%) were prescribed NSAIDs, although the median duration of use was relatively short (0.5 years; range, 0.2–4.6 years), and 37% of patients were prescribed statins (median duration, 5.3 years; range, 1.9–8.3 years). Both NSAIDs and statins were prescribed in 30% of patients.



After adjusting for age, gender, BE length, baseline histology, and use of other medications, NSAID use was found to be associated with a nearly 50% reduction in the risk of neoplastic progression (HR, 0.51; 95% CI, 0.26–1.00;  $P=.048$ ). Use of statins was associated with a risk reduction of 64% (HR, 0.36; 95% CI, 0.17–0.77;  $P=.009$ ). Use of both agents appeared to have the greatest protective effect; patients taking both NSAIDs and statins had an 81% reduction in the risk of HGD or EAC compared to patients taking neither drug (HR, 0.19; 95% CI, 0.07–0.50;  $P=.001$ ).

### Dietary Therapy Is Effective for Eosinophilic Esophagitis with Food Triggers

For individuals with eosinophilic esophagitis (EoE), food triggers can be identified by eliminating common food allergens in the diet and then reintroducing those allergens. However, the long-term efficacy of dietary intervention in adults is unknown. To evaluate this issue, Gonсалves and colleagues prospectively evaluated the effects of dietary intervention on histologic and symptomatic response after 1 year in individuals with EoE; results of this study were presented at DDW 2011.

A total of 50 patients (50% male) completed a 6-week course of the Six Food Elimination Diet (SFED). Of these 50 patients, 20 completed reintroduction and food trigger identification. Nine patients (5 males) then continued on a maintenance diet that avoided food triggers; after 1 year, these patients underwent endoscopy with proximal and distal esophageal biopsies, and symptoms were reassessed. The mean age of these 9 patients was 41 years (range, 22–56 years). Common food triggers included milk (55%), wheat (33%), nuts (33%), and seafood (11%); 4 patients had multiple food triggers.

Baseline endoscopy revealed rings in 98% of patients, furrows in 66% of patients, and plaques in 30% of patients. After 1 year of dietary restriction, endoscopic features appeared to be near normal, with the exception of subtle rings and furrows. In terms of symptoms, 8 of 9 patients were asymptomatic after 1 year, and the remaining patient had minimal symptoms. The investigators also reported a significant improvement in the median peak number of eosinophils per high-power field (eos/hpf) pre-SFED versus 6 weeks post-SFED in both the proximal biopsy (19 vs 0) and the distal biopsy (60 vs 0;  $P<.0001$  for both comparisons). The median peak number of eos/hpf after 1 year was 0 in the proximal biopsy ( $P=.01$  from baseline) and 6 in the distal biopsy ( $P<.001$  from baseline).

After 1 year of dietary therapy, all patients had at least partial resolution of EoE (>50% reduction in the

peak number of eos/hpf from baseline), 67% of patients had near complete resolution of EoE ( $\leq 10$  eos/hpf), and 33% of patients had complete resolution of EoE ( $\leq 5$  eos/hpf). Finally, the investigators noted that some patients had persistent low levels of esophageal eosinophils but lacked other features of active EoE, including epithelial hyperplasia. The clinical significance of the low levels of esophageal eosinophils is unknown.

Of the 11 patients who completed reintroduction and food trigger identification but were not included in the above analysis, 7 patients are currently completing the maintenance diet, and 4 patients opted for treatment with swallowed fluticasone instead of long-term diet therapy, as they felt the diet therapy was too restrictive (3 of these patients had  $\geq 3$  food triggers).

### Functional Disorders Predict Proton Pump Inhibitor Failure in GERD

To evaluate factors associated with response to PPI therapy in patients with GERD, Zerbib and colleagues prospectively studied 81 patients with typical GERD symptoms (without grade C/D esophagitis) who had been referred for pH-impedance monitoring. Results of this study were presented at DDW 2011.

Of the 81 patients included in the analysis, the median age was 50 years, and 42% of patients were male. Patients were studied off therapy. Overall, 43% of patients showed response to therapy (defined as having fewer than 2 days of mild symptoms weekly while on standard-dose or double-dose PPI therapy for at least 4 weeks). The remaining 57% of patients were nonresponders.

In a multivariate analysis of all evaluated patients, factors that were independently associated with lack of response to therapy included the absence of esophagitis, functional dyspepsia (FD) symptoms, and a BMI less than 25 kg/m<sup>2</sup>. Among the 67 patients who reported symptoms during the monitoring session, the only factors associated with lack of response were FD symptoms and a BMI less than 25 kg/m<sup>2</sup>. Finally, in the 49 patients with positive pH-impedance monitoring (such as 24-hour esophageal acid exposure >5% or a positive symptom association), the only factors associated with lack of response to therapy were FD symptoms and irritable bowel syndrome (IBS) symptoms.

The investigators concluded that nonerosive reflux disease is associated with lower response rates to PPI therapy and that FD predicts PPI failure even in the presence of pathologic gastroesophageal reflux. However, 24-hour pH-impedance monitoring revealed no baseline reflux parameters that could predict the likelihood of treatment failure.

# Presentations in IBS

## Ileal Bile Acid Transport Inhibitor Is Effective in Patients with Chronic Constipation

In an 8-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter, phase II study, Chey and colleagues evaluated the safety and efficacy of the ileal bile acid transport inhibitor A3309 in patients with chronic idiopathic constipation. Results of this study were presented at DDW 2011. This study enrolled 190 patients with functional constipation (as defined by the modified Rome III criteria) who had fewer than 3 complete spontaneous bowel movements (CSBMs) per week during the 2-week baseline period. Patients with primarily abdominal pain were excluded.

Patients were randomly assigned to receive A3309 (at a dose of 5 mg, 10 mg, or 15 mg once daily) or placebo. Patients' baseline characteristics were well balanced among study arms. The mean age of enrolled patients was 48 years; 90% of patients were female; and the average numbers of weekly spontaneous bowel movements (SBMs) and CSBMs were 2.82 and 0.4, respectively. Total cholesterol levels were above 200 mg/dL in 30% of patients at baseline.

The primary endpoint of the study, defined as the mean change in the number of SBMs during Week 1 compared to baseline, was significantly greater in patients treated with 10 mg or 15 mg of A3309 compared to placebo (4.0 and 5.4 vs 1.7;  $P < .01$  and  $P < .001$ , respectively). A3309 was also superior to placebo in terms of multiple secondary endpoints. In terms of symptoms, A3309 was associated with reductions in straining and bloating but not with pain/discomfort. The investigators also noted significant increases in bile acid synthesis (as assessed by measurement of 7-hydroxy-4-cholesten-3-one) and significant reductions in low-density lipoprotein cholesterol levels in patients receiving A3309.

Discontinuation rates were similar among the placebo group (12.8%), 5-mg A3309 group (12.5%), and 10-mg A3309 group (12.8%) but were higher in the 15-mg A3309 group (22.9%). Treatment-emergent adverse events occurred at rates of 44%, 46%, 62%, and 65%, respectively. The most frequent adverse events were abdominal pain (reported in 0%, 10%, 11%, and 25% of patients, respectively) and diarrhea (reported in 4%, 8%, 11%, and 17%, respectively). The investigators concluded that A3309 administered at a dose of 10 mg per day provided the best balance of efficacy and toxicity.

## Meta-Analysis Demonstrates Efficacy of Rifaximin in Irritable Bowel Syndrome

In a meta-analysis presented at DDW 2011, Menees and colleagues reviewed the efficacy and safety of the minimally absorbed antibiotic rifaximin in patients with IBS. This analysis included 1,803 patients with IBS (96% with nonconstipated IBS) who were enrolled across 5 randomized, placebo-controlled trials. Two separate researchers independently collected and analyzed all data and study information for each trial.

Overall, this meta-analysis found that rifaximin was superior to placebo in terms of the proportion of patients who attained global symptom improvement (42% vs 32%; odds ratio [OR], 1.57; 95% CI, 1.29–1.91;  $P = .0038$ ) and the proportion of patients with improvement in bloating (42% vs 32%; OR, 1.55; 95% CI, 1.27–1.89;  $P < .0001$ ); however, bloating was only evaluated in 4 studies. Other findings included a significant improvement in abdominal pain with rifaximin versus placebo (in 4 studies) and improvement in stool consistency with rifaximin (in 3 studies). The researchers did not find a dose-response relationship for rifaximin, nor was any publication bias apparent.

Rifaximin was well tolerated in these short-term trials (up to 10 weeks). The incidence of adverse events—both overall and serious adverse events—was similar for rifaximin and placebo. The most frequent adverse events were headache, upper respiratory infection, urinary tract infection, nausea, vomiting, and diarrhea; no adverse event occurred in more than 10% of patients. Moreover, serious adverse events occurred in less than 2% of patients, and no patients developed confirmed *Clostridium difficile*-associated diarrhea. The investigators concluded that these studies showed rifaximin to be well tolerated and more effective than placebo, at least for the limited duration over which they were evaluated.

## Mindfulness Training Is Effective in Reducing Irritable Bowel Syndrome Symptoms

Previous studies have demonstrated the ability of mindfulness training to improve symptoms in patients with chronic conditions such as fibromyalgia and depression. To determine the effects of mindfulness meditation training in patients with IBS, Gaylord and colleagues conducted a randomized controlled trial that was reported at DDW 2011. In

this study, 75 female patients with IBS (mean age, 43 years; range, 19–71 years) were randomly assigned to mindfulness training or a support group. Participants in both groups attended 8 weekly group sessions and a half-day retreat.

Both groups were similar in terms of baseline characteristics, including demographics, IBS severity score (IBS-SS), and IBS-related quality of life. Assessments after the first session showed that patients gave the 2 interventions similar credibility ratings. Overall, 66 patients completed their prescribed intervention (34 patients in the mindfulness training group and 32 patients in the support group), yielding a completion rate of 88%.

Using an intent-to-treat analysis, mindfulness training was found to be significantly more effective than a support group in terms of percent change in IBS-SS, both when assessed at the end of the intervention (25.4% vs 6.2%;  $P=.006$ ) and 3 months later (38.2% vs 11.8%;  $P=.001$ ). Although other outcomes—including quality of life, visceral anxiety, and psychological distress—were similar between the 2 groups at the end of treatment, these measures were improved to a greater extent after 3 months in the mindfulness training group compared to the support group. In the mindfulness training group, mindfulness scores increased significantly by the end of the intervention and remained elevated 3 months later. The investigators concluded that mindfulness training was effective for reducing IBS symptoms and improving quality of life; they also found that this therapeutic effect persisted several months after training had been completed.

### Once-Daily Linaclotide Is Effective Over 26 Weeks in Patients Who Have Irritable Bowel Syndrome with Constipation

In a randomized, double-blind, placebo-controlled, phase III trial presented by Chey and colleagues at DDW 2011, the efficacy and safety of the minimally absorbed guanylate cyclase-C receptor agonist linaclotide was evaluated in patients who had IBS with constipation (IBS-C). To be enrolled in this study, patients were required to meet the modified Rome II criteria for IBS-C; in addition, patients had to have an average of fewer than 3 CSBMs per week, 5 or fewer SBMs per week, and an abdominal pain score of 3 or greater on a 0–10 scale during the study's 2-week baseline period.

The intent-to-treat population included 804 patients; the group's median age was 44 years, and 90% of patients were female. During the 2-week baseline period, 87% of patients had abdominal pain every day (mean score, 5.6), and 76% of patients had no CSBMs (mean number of CSBMs per week, 0.2). Patients were randomly assigned

to receive 26 weeks of treatment with linaclotide (266 µg once daily; 401 patients) or placebo (403 patients).

All 4 primary endpoints and multiple secondary endpoints showed linaclotide to be significantly more effective than placebo, both over the first 12 weeks of the study and over the entire 26-week study period. Linaclotide was also associated with significant improvements in abdominal pain compared to placebo for each week of the 26-week study period.

The most frequent adverse event associated with linaclotide was diarrhea, although discontinuation of treatment due to diarrhea was rare (4.0% with linaclotide vs 0.2% with placebo). Overall, linaclotide was found to provide significant improvements in abdominal pain and bowel symptoms, and these improvements were sustained over 26 weeks.

### Psychological Factors Influence the Development of Functional Dyspepsia

To investigate the directionality of the brain-gut connection in IBS and FD, Koloski and colleagues conducted a prospective, longitudinal, population-based, cohort study, the results of which were presented at DDW 2011. In this study, the investigators evaluated the association among anxiety, depression, and the new onset of FD and IBS over a 12-year period in a randomly selected group of Australian patients. The analysis included individuals who had responded to a survey on functional gastrointestinal symptoms in 1997 and agreed to be contacted for additional research.

Of the 1,775 initial participants, a total of 1,002 completed the follow-up survey, yielding a response rate of 56%. During the 12-year follow-up period, new-onset IBS (as defined by the Rome II criteria) developed in 44 individuals, and new-onset FD developed in 23 individuals. Among participants who did not have a functional gastrointestinal disorder at baseline, the presence of clinically elevated psychological distress at baseline ( $\geq 4$  of 12 on the valid Delusions Symptom States Inventory) was associated with a significant increase in the risk of developing new-onset FD. This finding was true for both anxiety (OR, 2.7; 95% CI, 1.1–6.4;  $P=.03$ ) and depression (OR, 4.5; 95% CI, 1.7–11.6;  $P=.002$ ).

In contrast, neither anxiety nor depression was associated with an increased risk of new-onset IBS. However, the study found nonsignificant trends between IBS at baseline and the development of new clinical anxiety at the time of the follow-up survey (OR, 2.0; 95% CI, 0.9–4.6;  $P=.11$ ) or the development of any psychological distress (OR, 1.9; 95% CI, 0.8–4.3;  $P=.15$ ). The development of FD was not associated with anxiety or depression at the time of the follow-up survey.

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- VIREAD was evaluated in a limited number of subjects with chronic hepatitis B and decompensated liver disease
- The numbers of subjects in clinical trials who had lamivudine- or adefovir-associated substitutions at baseline were too small to reach conclusions of efficacy

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- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals**
- **Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including VIREAD. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including VIREAD. If appropriate, resumption of anti-hepatitis B therapy may be warranted**

\* Study 106 is an ongoing Phase 2 study involving Hepsera–treatment-experienced subjects previously treated for 24 to 96 weeks with Hepsera for chronic HBV infection and had plasma HBV DNA ≥1000 copies/mL at screening.<sup>1</sup>

† Study 108 was a small, double-blind, randomized, active-controlled trial comparing the safety of VIREAD and other oral antivirals in patients with CHB and decompensated liver disease through 48 weeks.<sup>1</sup>

Please see continued Important Safety Information and brief summary of full Prescribing Information for VIREAD on the following pages.

My liver.  My fight. My VIREAD.

# Important Safety Information (cont'd)

## Warnings and Precautions

- **New onset or worsening renal impairment:** New onset or worsening renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), have been reported with the use of VIREAD. Assess creatinine clearance (CrCl) before initiating treatment with VIREAD. Monitor CrCl and serum phosphorus in patients at risk, including those who have previously experienced renal events while receiving HEPSERA® (adefovir dipivoxil). Avoid administering VIREAD with concurrent or recent use of nephrotoxic drugs. Dosing interval adjustment of VIREAD and close monitoring of renal function are recommended in all patients with CrCl <50 mL/min
- **Coadministration with other products:**
  - Do not use with other tenofovir-containing products (eg, ATRIPLA® [efavirenz/emtricitabine/tenofovir disoproxil fumarate] and TRUVADA® [emtricitabine/tenofovir disoproxil fumarate])
  - Do not administer in combination with HEPSERA
- **Patients coinfecting with HIV-1 and HBV:** Due to the risk of development of HIV-1 resistance, VIREAD should only be used in HIV-1 and HBV coinfecting patients as part of an appropriate antiretroviral combination regimen. HIV antibody testing should be offered to all HBV-infected patients before initiating therapy with VIREAD
- **Decreases in bone mineral density:** Decreases in bone mineral density (BMD) have been observed in HIV-infected patients. Consider monitoring BMD in patients with a history of pathologic fracture or who are at risk for osteopenia. The bone effects of VIREAD have not been studied in patients with chronic HBV infection. Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of VIREAD

## Adverse Reactions

- **In HBV-infected patients with compensated liver disease:** Most common adverse reaction (all grades) was nausea (9%). Other treatment-emergent adverse reactions reported in >5% of patients treated with VIREAD included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain, and skin rash
- **In HBV-infected patients with decompensated liver disease:** Most common adverse reactions (all grades) reported in ≥10% of patients treated with VIREAD were abdominal pain (22%), nausea (20%), insomnia (18%), pruritus (16%), vomiting (13%), dizziness (13%), and pyrexia (11%)

Please see full Indication and Important Safety Information for VIREAD, including **boxed WARNING** information about **lactic acidosis, severe hepatomegaly with steatosis, and post treatment exacerbation of hepatitis**, on preceding page.

**References:** 1. VIREAD Prescribing Information. Foster City, CA: Gilead Sciences, Inc.; October 2010. 2. Study 102, Data on file, Gilead Sciences, Inc. 3. Study 103, Data on file, Gilead Sciences, Inc. VIREAD, HEPSERA, and TRUVADA are registered trademarks of Gilead Sciences, Inc. ATRIPLA is a registered trademark of Bristol-Myers Squibb & Gilead Sciences, LLC.

## Drug Interactions

- **Didanosine:** Coadministration increases didanosine concentrations. Use with caution and monitor for evidence of didanosine toxicity (eg, pancreatitis, neuropathy). Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions. In adults weighing >60 kg, the didanosine dose should be reduced to 250 mg when it is coadministered with VIREAD. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg
- **Atazanavir:** Coadministration decreases atazanavir concentrations and increases tenofovir concentrations. Use atazanavir with VIREAD only with additional ritonavir; monitor for evidence of tenofovir toxicity
- **Lopinavir/ritonavir:** Coadministration increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity

## Dosage and Administration

- The recommended dose for the treatment of chronic hepatitis B: 300 mg once daily taken orally without regard to food. In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown
- The dosing interval of VIREAD should be adjusted (using recommendations in the table below) and renal function closely monitored in patients with creatinine clearance <50 mL/min

## Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine clearance (mL/min) <sup>a</sup>			Hemodialysis patients
	≥50	30-49	10-29	
<b>Recommended 300 mg dosing interval</b>	Every 24 hours	Every 48 hours	Every 72 to 96 hours	Every 7 days or after a total of approximately 12 hours of dialysis <sup>b</sup>

<sup>a</sup> Calculated using ideal (lean) body weight.

<sup>b</sup> Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours' duration. VIREAD should be administered following completion of dialysis.

- The pharmacokinetics of tenofovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10 mL/min; therefore, no dosing recommendation is available for these patients
- No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance 50-80 mL/min). Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in these patients

# VIREAD® (tenofovir disoproxil fumarate) Tablets

Brief summary of full prescribing information. Please see full prescribing information including Boxed WARNINGS. Rx only

**WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT EXACERBATION OF HEPATITIS**

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals (See Warnings and Precautions).
- Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including VIREAD. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including VIREAD. If appropriate, resumption of anti-hepatitis B therapy may be warranted (See Warnings and Precautions).

**INDICATIONS AND USAGE:** VIREAD is indicated for the treatment of chronic hepatitis B in adults. The following points should be considered when initiating therapy with VIREAD for the treatment of HBV infection:

- This indication is based primarily on data from treatment of subjects who were nucleoside-treatment-naïve and a smaller number of subjects who had previously received lamivudine or adefovir dipivoxil. Subjects were adults with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease (See Adverse Reactions).
- VIREAD was evaluated in a limited number of subjects with chronic hepatitis B and decompensated liver disease.
- The numbers of subjects in clinical trials who had lamivudine- or adefovir-associated substitutions at baseline were too small to reach conclusions of efficacy.

**DOSE AND ADMINISTRATION:** For the treatment of chronic hepatitis B in adults, the dose is one 300 mg VIREAD tablet once daily taken orally, without regard to food. The optimal duration of treatment is unknown. **Dose Adjustment for Renal Impairment in Adults:** Significantly increased drug exposures occurred when VIREAD was administered to subjects with moderate to severe renal impairment. Therefore, the dosing interval of VIREAD should be adjusted in patients with baseline creatinine clearance <50 mL/min using the recommendations in Table 1. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV and non-HBV infected subjects with varying degrees of renal impairment, including end-stage renal disease requiring hemodialysis. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in patients with moderate or severe renal impairment, therefore clinical response to treatment and renal function should be closely monitored in these patients (See Warnings and Precautions). No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance 50–80 mL/min). Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients with mild renal impairment (See Warnings and Precautions).

Table 1 Dosing Adjustment for Adult Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min) <sup>a</sup>			Hemodialysis Patients
	≥50	30-49	10-29	
<b>Recommended 300 mg Dosing Interval</b>	Every 24 hours	Every 48 hours	Every 72 to 96 hours	Every 7 days or after a total of approximately 12 hours of dialysis <sup>b</sup>

- Calculated using ideal (lean) body weight.
- Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration. VIREAD should be administered following completion of dialysis.

The pharmacokinetics of tenofovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10 mL/min; therefore, no dosing recommendation is available for these patients. No data are available to make dose recommendations in pediatric patients 12 years of age and older with renal impairment.

**CONTRAINDICATIONS:** None.

**WARNINGS AND PRECAUTIONS: Lactic Acidosis/Severe Hepatomegaly with Steatosis:** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with VIREAD should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations). **Exacerbation of Hepatitis after Discontinuation of Treatment:** Discontinuation of anti-HBV therapy, including VIREAD, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue VIREAD should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted. **New Onset or Worsening Renal Impairment:** Tenofovir is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of VIREAD (See Adverse Reactions). It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with VIREAD. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment, including patients who have previously experienced renal events while receiving HEPSERA. Dosing interval adjustment of VIREAD and dose monitoring of renal function are recommended in all patients with creatinine clearance <50 mL/min (See Dosage and Administration). No safety or efficacy data are available in patients with renal impairment who received VIREAD using these dosing guidelines, so the potential benefit of VIREAD therapy should be assessed against the potential risk of renal toxicity. VIREAD should be avoided with concurrent or recent use of a nephrotoxic agent. **Coadministration with Other Products:** VIREAD should not be used in combination with the fixed-dose combination products TRUVADA® (emtricitabine/tenofovir disoproxil fumarate) or ATRIPLA® (efavirenz/emtricitabine/tenofovir disoproxil fumarate) since tenofovir disoproxil fumarate is a component of these products. VIREAD should not be administered in combination with HEPSERA® (adefovir dipivoxil) (See Drug Interactions). **Patients Coinfected with HIV-1 and HBV:** Due to the risk

of development of HIV-1 resistance, VIREAD (tenofovir disoproxil fumarate) should only be used in HIV-1 and HBV coinfecting patients as part of an appropriate antiretroviral combination regimen. HIV-1 antibody testing should be offered to all HBV-infected patients before initiating therapy with VIREAD. It is also recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B before initiating treatment with VIREAD.

**Decreases in Bone Mineral Density:** Assessment of bone mineral density (BMD) should be considered for adults and pediatric patients 12 years of age and older who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained. In HIV-infected adult subjects treated with VIREAD in Study 903 through 144 weeks, decreases from baseline in BMD were seen at the lumbar spine and hip in both arms of the study. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving VIREAD + lamivudine + efavirenz (-2.2% ± 3.9) compared with subjects receiving stavudine + lamivudine + efavirenz (-1.0% ± 4.6). Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the VIREAD group vs. -2.4% ± 4.5 in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the study and this reduction was sustained through Week 144. Twenty-eight percent of VIREAD-treated subjects vs. 21% of the stavudine-treated subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the VIREAD group and 6 subjects in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide) in the VIREAD group relative to the stavudine group, suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in the VIREAD group. Except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range. In a clinical study of HIV-1 infected pediatric subjects 12 years of age and older (Study 321), bone effects were similar to adult subjects. Under normal circumstances BMD increases rapidly in this age group. In this study, the mean rate of bone gain was less in the VIREAD-treated group compared to the placebo group. Six VIREAD-treated subjects and one placebo-treated subject had significant (>4%) lumbar spine BMD loss in 48 weeks. Among 28 subjects receiving 96 weeks of VIREAD, Z-scores declined by -0.341 for lumbar spine and -0.458 for total body. Skeletal growth (height) appeared to be unaffected. Markers of bone turnover in VIREAD-treated pediatric subjects 12 years of age and older suggest increased bone turnover, consistent with the effects observed in adults. The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of VIREAD (See Adverse Reactions). The bone effects of VIREAD have not been studied in patients with chronic HBV infection.

## VIREAD 170 SEPT PG 6

**ADVERSE REACTIONS: Clinical Trials in Adult Subjects with Chronic Hepatitis B and Compensated Liver Disease:** Treatment-Emergent Adverse Reactions: In controlled clinical trials in subjects with chronic hepatitis B (n=202 and n=202), subjects treated with VIREAD during the 48-week double-blind period experienced nausea: 9% with VIREAD versus 2% with HEPSERA. Other treatment-emergent adverse reactions reported in >5% of subjects treated with VIREAD included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain, and skin rash. No significant change in the tolerability profile (nature or severity of adverse reactions) was observed in subjects continuing treatment with VIREAD for up to 144 weeks in these studies.

**Laboratory Abnormalities:** A summary of Grade 3 and 4 laboratory abnormalities through Week 48 is provided in Table 2. Grade 3/4 laboratory abnormalities were similar in subjects continuing VIREAD treatment for up to 144 weeks in these studies.

Table 2 Grade 3/4 Laboratory Abnormalities Reported in ≥1% of VIREAD-Treated Chronic Hepatitis B Subjects in Studies 0102 and 0103 (0-48 Weeks)

	VIREAD (N=426)	HEPSERA (N=215)
Any ≥Grade 3 Laboratory Abnormality	19%	13%
Creatine Kinase (M: >990 U/L; F: >845 U/L)	2%	3%
Serum Amylase (>175 U/L)	4%	1%
Glycosuria (≥3+)	3%	<1%
AST (M: >180 U/L; F: >170 U/L)	4%	4%
ALT (M: >215 U/L; F: >170 U/L)	10%	6%

The overall incidence of on-treatment ALT flares (defined as serum ALT >2 × baseline and >10 × ULM, with or without associated symptoms) was similar between VIREAD (2.6%) and HEPSERA (2%). ALT flares generally occurred within the first 4–8 weeks of treatment and were accompanied by decreases in HBV DNA levels. No subject had evidence of decompensation. ALT flares typically resolved within 4 to 8 weeks without changes in study medication.

**Clinical Trial in Adult Subjects with Chronic Hepatitis B and Decompensated Liver Disease:** In a small randomized, double-blind, active-controlled trial (0108), subjects with CHB and decompensated liver disease received treatment with VIREAD or other antiviral drugs for up to 48 weeks. Among the 45 subjects receiving VIREAD, the most frequently reported treatment-emergent adverse reactions of any severity were abdominal pain (22%), nausea (20%), insomnia (18%), pruritus (16%), vomiting (13%), dizziness (13%), and pyrexia (11%). Two of 45 (4%) subjects died through Week 48 of the study due to progression of liver disease. Three of 45 (7%) subjects discontinued treatment due to an adverse event. Four of 45 (9%) subjects experienced a confirmed increase in serum creatinine of 0.5 mg/dL (1 subject also had a confirmed serum phosphorus <2 mg/dL through Week 48). Three of these subjects (each of whom had a Child-Pugh score ≥10 and MELD score ≥14 at entry) developed renal failure. Because both VIREAD and decompensated liver disease may have an impact on renal function, the contribution of VIREAD to renal impairment in this population is difficult to ascertain. One of 45 subjects experienced an on-treatment hepatic flare during the 48 week study.

**Postmarketing Experience:** The following adverse reactions have been identified during postapproval use of VIREAD. 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: allergic reaction, including angioedema, lactic acidosis, hypokalemia, hypophosphatemia, dyspnea, pancreatitis, increased amylase, abdominal pain, hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT), rash, rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy, acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria, asthenia. The following adverse reactions listed above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

**DRUG INTERACTIONS: Didanosine:** Coadministration of VIREAD and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions. When administered with VIREAD, C<sub>max</sub> and AUC of didanosine (administered as either the buffered or enteric-coated formulation) increased significantly. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis and neuropathy. Suppression of CD4+ cell counts has been observed in patients receiving tenofovir disoproxil fumarate (tenofovir DF) with didanosine 400 mg daily. In patients weighing >60 kg, the didanosine dose should be reduced to 250 mg when it is coadministered with VIREAD. Data are not available to recommend a dose adjustment of didanosine for adult or pediatric patients weighing <60 kg. When coadministered, VIREAD and didanosine EC may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). Coadministration of didanosine buffered tablet formulation with VIREAD should be under fasted conditions. **Atazanavir:** Atazanavir has been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving atazanavir and VIREAD should be monitored for VIREAD-associated adverse reactions. VIREAD should be discontinued in patients who develop VIREAD-associated adverse reactions. VIREAD decreases the AUC and C<sub>min</sub> of atazanavir. When coadministered with VIREAD, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Atazanavir without ritonavir should not be coadministered with VIREAD. **Lopinavir/Ritonavir:** Lopinavir/ritonavir has been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving lopinavir/ritonavir and VIREAD should be monitored for VIREAD-associated adverse reactions. VIREAD should be discontinued in patients who develop VIREAD-associated adverse reactions. **Drugs Affecting Renal Function:** Since tenofovir is primarily eliminated by the kidneys, coadministration of VIREAD with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to, cidofovir, acyclovir, valacyclovir, ganciclovir, and valganciclovir. Drugs that decrease renal function may also increase serum concentrations of tenofovir. In the treatment of chronic hepatitis B, VIREAD should not be administered in combination with HEPSERA (adefovir dipivoxil).

**USE IN SPECIFIC POPULATIONS: Pregnancy: Pregnancy Category B:** Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, VIREAD (tenofovir disoproxil fumarate) should be used during pregnancy only if clearly needed. **Antiretroviral Pregnancy Registry:** To monitor fetal outcomes of pregnant women exposed to VIREAD, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

**Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1.** Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir is excreted in human milk. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving VIREAD.** **Geriatric Use:** Clinical studies of VIREAD did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. **Patients with Impaired Renal Function:** It is recommended that the dosing interval for VIREAD be modified in patients with creatinine clearance <50 mL/min or in patients with end-stage renal disease (ESRD) who require dialysis (See Dosage and Administration).

**NONCLINICAL TOXICOLOGY: Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose. Tenofovir disoproxil fumarate was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, tenofovir disoproxil fumarate was negative when administered to male mice. There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats. **Animal Toxicology and/or Pharmacology:** Tenofovir and tenofovir disoproxil fumarate administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) greater than or equal to 6 fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown. Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calcemia and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2–20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

For detailed information, please see full prescribing information. To learn more: call 1-800-GILEAD-5 (1-800-445-3235) or visit [www.VIREAD.com](http://www.VIREAD.com). TRUVADA, EMTRIVA, HEPSERA, and VIREAD are registered trademarks of Gilead Sciences, Inc. ATRIPLA is a trademark of Bristol-Myers Squibb & Gilead Sciences, LLC. All other trademarks referenced herein are the property of their respective owners.

REFERENCE: 1. VIREAD® (tenofovir disoproxil fumarate) Prescribing Information. Foster City, CA: Gilead Sciences, Inc.; October 2010.



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# Presentations in Hepatology

## Response-Guided Therapy Is Effective in Boceprevir-Treated Patients

Response-guided therapy involves modifying total treatment duration based on whether patients attain hepatitis C virus (HCV) RNA undetectability early in the course of therapy. Two large studies, SPRINT-2 and RESPOND-2, included response-guided therapy arms to test the efficacy of such treatment regimens; the duration of treatment was determined based on virologic responses at Weeks 8 and 12 in RESPOND-2 and at Weeks 8–24 in SPRINT-2. In an analysis presented at DDW 2011, Manns and colleagues further analyzed the outcomes from both of these response-guided therapy arms.

In the SPRINT-2 trial, 57% of patients (208 of 368) in the response-guided therapy arm had undetectable levels of HCV RNA at Week 8. These early responders received treatment for a total duration of 28 weeks; 88% of these patients achieved sustained virologic response (SVR), compared to an SVR rate of 90% in the patients who received 4 weeks of peginterferon and ribavirin followed by 44 weeks of boceprevir-based triple therapy. Most subgroup analyses showed similar SVR rates for response-guided therapy compared to 48 weeks of boceprevir-based triple therapy; an exception occurred in patients with advanced fibrosis, in whom SVR rates were higher among patients who received 48 weeks of boceprevir-based triple therapy. However, there were fewer than 15 patients per group in this category.

In the RESPOND-2 trial, which enrolled patients who had previously failed treatment, 46% of patients (74 of 162) in the response-guided therapy arm achieved undetectable levels of HCV RNA by Week 8 and maintained HCV undetectability at Week 24, making these patients eligible for a shortened course of therapy. These patients received treatment for a total duration of 36 weeks and achieved an SVR rate of 86%. The SVR rate in patients treated with 48 weeks of boceprevir-based triple therapy was 88%. Only 2 subgroups showed lower SVR rates with response-guided therapy compared to 48 weeks of boceprevir-based triple therapy: previous nonresponders to peginterferon and ribavirin (78% vs 90%) and patients with advanced fibrosis (80% vs 90%).

Based on their analysis, Manns and colleagues suggested that response-guided therapy may be preferable to fixed-duration treatment both in previously untreated patients and in patients who previously failed treatment, as response-guided therapy provides comparable efficacy with a shorter treatment duration.

## Telaprevir May Extend Patients' Life Span and Reduce Long-Term Complications Associated with HCV Infection

To assess the potential long-term clinical value of telaprevir-based therapy in patients with genotype 1 HCV infection, Brogan and colleagues used Microsoft Excel to develop a decision-analytic model with a treatment phase and a post-treatment phase that could estimate long-term outcomes following treatment with telaprevir plus peginterferon and ribavirin versus peginterferon and ribavirin alone. Results of this analysis were presented during DDW 2011.

The patient population included in the model consisted of a group of treatment-naïve patients and a group of treatment-experienced patients who had received prior therapy with peginterferon and ribavirin. Patients were modeled through a 72-week decision-tree treatment phase mirroring the ADVANCE and REALIZE clinical trials, after which they were moved through a long-term post-treatment phase. The probability of adverse clinical outcomes and mortality risks were obtained from the published literature and US life tables.

According to this model, telaprevir-based therapy would extend patients' life span by an average of 2.0 years in treatment-naïve patients and 3.4 years in treatment-experienced patients, compared to treatment with peginterferon and ribavirin alone. Quality-adjusted life-years would be extended by 2.4 years and 3.8 years, respectively.

Over patients' remaining lifetime, telaprevir-based therapy would be expected to reduce the risk of compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, and liver transplantation by approximately half compared to treatment with peginterferon and ribavirin alone. Telaprevir-based therapy would also reduce the risk of HCV-related death by nearly half: from 24.8% to 12.6% in treatment-naïve patients, and from 42.0% to 21.6% in treatment-experienced patients.

## Boceprevir-Based Triple Therapy Is Effective in Some Prior Nonresponders and Relapsers

The RESPOND-2 trial evaluated boceprevir plus peginterferon and ribavirin in patients who had failed prior treatment; patients in this study included prior nonresponders (patients who had an HCV RNA reduction  $\geq 2.0 \log_{10}$  by Week 12 but who did not achieve HCV RNA undetectability) and prior relapsers (patients

who attained undetectable levels of HCV RNA at the end of treatment but who did not subsequently attain SVR). In a study presented at DDW 2011, Esteban and colleagues compared patients' historical response to peginterferon and ribavirin with the response to peginterferon and ribavirin observed during the 4-week lead-in period of the RESPOND-2 trial.

Among the 144 nonresponders in the RESPOND-2 trial, SVR rates were 52% in patients who received 4 weeks of peginterferon and ribavirin followed by 44 weeks of boceprevir-based triple therapy, 40% in patients who received response-guided therapy, and 7% in patients who received peginterferon and ribavirin alone. SVR rates among the 259 relapsers were 75%, 69%, and 29%, respectively. In an exploratory analysis, an HCV RNA reduction of at least  $0.91 \log_{10}$  at Week 4 was found to be most predictive of SVR among boceprevir-treated patients.

Interestingly, many patients with a well-documented history of previous interferon responsiveness did not attain a decline in HCV RNA level of at least  $1.0 \log_{10}$  by Week 4 of the RESPOND-2 trial. Of the 394 patients with available data, 102 patients (26%) had a decline in HCV RNA level that was less than  $1.0 \log_{10}$  at Week 4. This poor interferon response was more common in historical nonresponders than in historical relapsers (39% vs 18%).

Despite the significant association between lower SVR rates and a less-than- $0.91 \log_{10}$  reduction in HCV RNA level at Week 4, the authors suggested that HCV RNA response following the 4-week lead-in period should not be used to define futility, as 33–34% of patients with an HCV RNA decline less than  $1.0 \log_{10}$  at Week 4 were able to attain SVR when treated with boceprevir plus peginterferon and ribavirin. Finally, a multivariate analysis found that Week 4 response to peginterferon and ribavirin (HCV RNA reduction  $\geq 1.0 \log_{10}$  vs  $< 1.0 \log_{10}$ ) was a stronger predictor of SVR than historical treatment response.

### Hepatitis B Virus Genotype and Hepatitis B Surface Antigen Levels Predict Hepatitis B e Antigen Seroconversion in Patients Treated with Tenofovir

In another study from DDW 2011, Heathcote and colleagues presented results of an analysis in which they evaluated baseline factors associated with hepatitis B e antigen (HBeAg) seroconversion in patients with HBeAg-positive chronic hepatitis B virus (HBV) infection who were receiving tenofovir disoproxil fumarate (TDF). The analysis included 259 patients enrolled in Study 103, the pivotal, phase III study of TDF in HBeAg-positive patients with chronic HBV infection.

In this double-blind trial, patients with HBeAg-positive chronic HBV infection were randomly assigned 2:1 to receive once-daily TDF (300 mg) or adefovir dipivoxil (ADV; 10 mg). After Week 48, eligible patients switched to open-label TDF for up to 7 additional years. Starting at Week 72, patients with confirmed HBV DNA levels at or above 400 copies/mL could add emtricitabine in a fixed-dose tablet. Patients with HBeAg seroconversion continued treatment until hepatitis B surface antigen (HBsAg) loss or seroconversion occurred.

A total of 104 enrolled patients (40%) attained HBeAg seroconversion at least once during the 192-week study period; 155 patients (60%) did not attain HBeAg seroconversion. The mean time to first HBeAg seroconversion was 69 weeks. At the time of HBeAg seroconversion, the mean decline in HBsAg level was  $1.01 \log_{10}$  IU/mL. The mean decline in HBV DNA level was  $5.99 \log_{10}$  copies/mL, and the mean change in alanine aminotransferase (ALT) level was  $-123.2$  U/L.

In a multivariate, stepwise analysis, 2 baseline characteristics were independently associated with HBeAg seroconversion: HBV genotype and HBsAg level. Seroconversion rates were highest in patients infected with HBV genotype A (37%) and lower in patients with genotypes B, C, and D (8%, 21%, and 27%, respectively;  $P < .001$  overall). The mean HBsAg level was  $4.38 \log_{10}$  IU/mL in patients who attained HBeAg seroconversion and  $4.54 \log_{10}$  IU/mL in patients who did not attain HBeAg seroconversion (OR for HBsAg titer, 0.52; 95% CI, 0.32–0.84;  $P = .006$ ). Other baseline characteristics—including race, gender, HBV DNA level, ALT level, and Knodell score—were not significantly associated with the likelihood of HBeAg seroconversion.

Over the study period, the investigators reported an increase in rates of HBsAg loss among patients with HBeAg seroconversion. At Week 48, HBsAg loss had occurred in 7.2% of HBeAg-seroconverted patients in the TDF-TDF arm and 0% of seroconverted patients in the ADV-TDF arm. These rates increased to 12.9% and 9.7%, respectively, at Week 96; 13.8% and 11.1%, respectively, at Week 144; and 18% and 7.7%, respectively, at Week 192.

### Breath Ammonia Testing Holds Promise as a Diagnostic Test for Hepatic Encephalopathy

Given the association between ammonia levels and hepatic encephalopathy (HE), researchers have considered using breath ammonia testing as a tool for diagnosing HE. To evaluate the feasibility of breath ammonia testing in this setting, Adrover and colleagues compared breath ammonia levels among 3 groups: healthy individuals, cirrhotic patients without overt HE (OHE), and



cirrhotic patients with OHE. Results of this study were presented at the 2011 Annual Meeting of the European Association for the Study of the Liver (EASL).

The evaluable study population included 106 subjects: 55 patients with cirrhosis and 51 healthy controls. Healthy controls were significantly younger than patients with cirrhosis (mean age, 44 years vs 58 years;  $P<.001$ ), but there were no significant differences between the 2 groups in terms of gender, average body weight, or BMI. Cirrhotic patients with OHE and those without OHE did not differ in terms of gender, mean age, or mean BMI.

Among healthy controls, the mean breath ammonia level was 151.4 parts per billion (ppb); this value did not differ significantly based on gender or age. Mean breath ammonia levels were significantly higher in patients with cirrhosis compared to controls (169.9 ppb vs 151.4 ppb;  $P=.00001$ ). In addition, mean breath ammonia levels were significantly higher in cirrhotic patients with grade 1–2 OHE compared to cirrhotic patients without OHE (184.1 ppb vs 162.9 ppb;  $P=.0011$ ). To differentiate between healthy individuals and patients with cirrhosis, the investigators assessed the area under the receiver operating characteristic curve and identified a cutoff value of 165 ppb. Among patients with cirrhosis, a cutoff value of 175 ppb was found to differentiate between patients with OHE and those without OHE.

Subgroup analyses of the patients with cirrhosis found no differences in the frequency of OHE or breath ammonia levels according to disease severity as assessed by Model for End-Stage Liver Disease scores ( $<15$  points vs  $\geq 15$  points)—either overall or based on gender, age, or BMI. When patients with cirrhosis were subdivided by Child-Pugh scores ( $<8$  points vs  $\geq 8$  points), a significant difference in the prevalence of OHE was observed ( $P=.026$ ), but the difference in breath ammonia levels between these 2 groups was not significant. The investigators concluded that breath ammonia testing appears to be feasible and useful, but further studies are needed to validate this technique.

### Rifaximin Is Effective for Maintenance of Remission in Patients with Overt Hepatic Encephalopathy

In 2010, Bass and colleagues published results of a randomized, double-blind, placebo-controlled trial in which they showed that rifaximin can significantly reduce the

risk of an HE episode over a 6-month period in cirrhotic patients who were in remission from recurrent HE (*N Engl J Med.* 2010;362:1071-1081). To further investigate the efficacy and safety of rifaximin for management of HE, Mullen and colleagues subsequently conducted an open-label maintenance trial of rifaximin (550 mg twice daily); results of this latter study were presented at the 2011 EASL meeting.

Both trials enrolled patients with a history of HE associated with cirrhosis or portal hypertension. In the randomized controlled trial, 299 patients were assigned 1:1 to receive 6 months of treatment with rifaximin (550 mg twice daily; 140 patients) or placebo (159 patients). In the subsequent open-label study, all patients received rifaximin (550 mg twice daily), and follow-up visits were scheduled every 3 months. Concomitant lactulose use was permitted in both studies. In the current analysis, the investigators reported outcomes from both studies independently, as well as from the population of 392 patients who were assigned to rifaximin in any part of the 2 trials.

Across both studies, the mean duration of drug exposure among rifaximin-treated patients was 476 days, yielding a total of 510 person-exposure years. Overall, rifaximin was associated with a 58% reduction in the risk of an HE breakthrough event compared to placebo (HR, 0.42; 95% CI, 0.28–0.64;  $P<.0001$ ). HE event rates—calculated as the number of events per person-exposure years of study drug—ranged from 0.24–0.40 in patients who received rifaximin to 1.6 in placebo-treated patients.

In the pooled analysis, rifaximin treatment was associated with a significant reduction in rates of hospitalization due to any cause (0.45 vs 1.31 events per person-exposure years for rifaximin and placebo, respectively;  $P<.0001$ ) and rates of HE-related hospitalizations (0.21 vs 0.72, respectively;  $P<.0001$ ). Rifaximin was also associated with lower rates of adverse events compared to placebo (0.71 vs 2.8), as well as lower rates of drug-related adverse events (0.11 vs 0.74), serious adverse events (0.48 vs 1.4), and discontinuations due to adverse events (0.25 vs 0.98). Rifaximin was not associated with an increase in mortality rates. The investigators concluded that rifaximin provided long-term protection from HE breakthrough and reduced rates of hospitalization without adversely affecting patient survival.

# Presentations in IBD

## Cyclosporine and Infliximab Are Both Effective for Steroid-Refractory Severe Acute Ulcerative Colitis

Intravenous (IV) corticosteroids are typically the first-line therapy for severe acute ulcerative colitis (UC), but medical rescue therapy may be necessary if patients do not respond to corticosteroids within 3–5 days. To determine whether IV cyclosporine or IV infliximab is more effective as rescue therapy in patients with steroid-resistant acute severe UC, Laharie and colleagues evaluated 111 patients with acute severe UC who were treated at 29 centers between June 2007 and August 2010. This study, which was presented at DDW 2011, was the first randomized controlled trial comparing cyclosporine and infliximab in this population.

Patients who fulfilled the criteria for IV steroid failure were randomized to receive either IV cyclosporine (2 mg/kg/d for 1 week, followed by oral cyclosporine through Day 98; n=55) or IV infliximab (5 mg/kg at Weeks 0, 2, and 6; n=56). In patients who showed a clinical response at Day 7 of rescue therapy, azathioprine was started at a dose of 2.5 mg/kg/d, and steroids were tapered according to a fixed regimen.

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

Rates of treatment failure were found to be similar in both treatment groups: 60% with cyclosporine versus 54% with infliximab. Response rates at Day 7 were also similar for both groups: 84% with cyclosporine versus 86% with infliximab. By Day 98, colectomies had been performed in 10 patients treated with cyclosporine and 13 patients treated with infliximab.

During the course of the study, 10 severe adverse events occurred in 9 patients treated with cyclosporine, and 16 serious adverse events occurred in 16 patients receiving infliximab. No deaths occurred in this study. The researchers concluded that cyclosporine is no more effective than infliximab for achieving short-term remission and avoiding urgent colectomy in acute severe UC patients who are refractory to IV corticosteroids.

## Assessing the Safety of Infliximab and Other Crohn's Disease Therapies

To determine the long-term safety of infliximab and other agents used in the treatment of Crohn's disease (CD), Lichtenstein and coworkers examined data from 6,273 patients enrolled in the TREAT registry; this analysis was presented at DDW 2011. This study included 3,420 individuals who received infliximab and 2,853 patients who received other medical therapies; the mean follow-up period was 5.2 years.

Mortality was similar for both infliximab-treated patients and patients who received other therapies (0.56 vs 0.62 deaths per 100 patient-years; risk ratio [RR], 0.91; 95% CI, 0.68–1.21). An adjusted Cox proportional hazards analysis showed that increased mortality risk was associated with the use of prednisone (HR, 2.113; 95% CI, 1.418–3.148;  $P<.001$ ) and use of narcotics (HR, 1.782; 95% CI, 1.197–2.655;  $P<.001$ ). In contrast, the association between increased mortality risk and disease severity (moderate/severe) was not statistically significant.

The incidence of malignancies was similar in both groups: 0.43 versus 0.52 per 100 patient-years among infliximab-treated patients and patients who did not receive infliximab, respectively (RR, 0.83; 95% CI, 0.61–1.14). The incidence of lymphoma was also similar between the 2 groups: 0.05 versus 0.06 per 100 patient-years, respectively (RR, 0.80; 95% CI, 0.31–2.07). An adjusted Cox analysis using medication exposure at any time prior to the event showed that infliximab treatment approached statistical significance as a predictor of serious infections (HR, 1.277; 95% CI, 0.977–1.668;  $P=.073$ ). Other factors associated with serious infections included use of prednisone (HR, 1.460; 95% CI, 1.141–1.870;  $P=.003$ ) and use of narcotics (HR, 1.732; 95% CI, 1.339–2.241;  $P<.001$ ). Using a multivariate Cox proportional hazards regression model and examining medication exposure in the prior 6-month data collection period, the study identified several significant predictors of serious infections: severity of disease (HR, 2.239; 95% CI, 1.569–3.194;  $P<.001$ ), use of narcotic analgesics (HR, 1.98; 95% CI, 1.436–2.729;  $P<.001$ ), use of prednisone (HR, 1.571; 95% CI, 1.173–2.103;  $P=.002$ ), and use of infliximab (HR, 1.431; 95% CI, 1.110–1.844;  $P=.006$ ).

Overall, infliximab-treated patients had similar rates of mortality and malignancy—including lymphoma—compared to patients who were not treated with

infiximab. Although patients treated with infiximab did show an increased risk of serious infections, Cox proportional hazards analyses suggest that this risk is most strongly associated with disease severity and the use of prednisone and/or narcotics.

### **Certolizumab Pegol Can Achieve Long-Term Remission in Patients with Crohn's Disease**

In another study presented at DDW 2011, Sandborn and colleagues assessed remission rates in patients who received long-term therapy with certolizumab pegol. Patients who completed the PRECiSE 2 study (during which they received 26 weeks of certolizumab pegol) were eligible to enter PRECiSE 3, during which they received 400 mg certolizumab pegol every 4 weeks for an additional 4.5 years. Efficacy and safety data for patients who received certolizumab pegol in PRECiSE 2 and continued with open-label treatment in PRECiSE 3 were presented in this study. The Harvey-Bradshaw Index (HBI) was used to measure disease activity, and remission was defined as an HBI score less than or equal to 4. Using PRECiSE 2 as a baseline, remission rates were analyzed in both the PRECiSE 3 intent-to-treat population and in a subset of PRECiSE 3 patients who had never received infiximab.

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

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

### **Would Weight-Based Dosing Improve Efficacy of Adalimumab and/or Certolizumab Pegol?**

Currently, infiximab, adalimumab, and certolizumab pegol are all approved for treatment of CD. A potentially important difference among these drugs is that infiximab is dosed based on a patient's weight, while certolizumab pegol and adalimumab do not employ weight-based dosing. To assess whether a patient's weight influences the efficacy of treatment with adalimumab and/or certolizumab pegol, Blonski and colleagues analyzed data from over 2,000 patients; results of this analysis were presented during DDW 2011.

All outpatient records in an electronic database were retrospectively reviewed to identify CD patients who had been treated with adalimumab and/or certolizumab pegol between October 1998 and October 2010. Adalimumab was administered subcutaneously at a dose of 160 mg at Week 0, 80 mg at Week 2, and 40 mg every other week thereafter (or weekly, if needed). Certolizumab pegol (400 mg) was administered subcutaneously at Weeks 0, 2, and 4, followed by maintenance doses every 4 weeks thereafter. Clinical response was defined as a reduction in HBI score of at least 3 points from baseline, and clinical remission was defined as an HBI score less than or equal to 4.

A total of 2,177 consecutively treated CD patients were identified. Eighty-four patients had been treated with adalimumab and/or certolizumab pegol. Of these 84 patients, 58 (69%) had been treated with adalimumab alone, 3 (4%) had received certolizumab pegol alone, and 23 (27%) had received adalimumab followed by certolizumab pegol. Of the 58 patients treated with adalimumab alone, 26 (45%) responded to the drug, 16 maintained remission, and 16 did not respond. Of the 3 patients treated with certolizumab pegol alone, 2 responded, and 1 did not respond. Of the 23 patients who received adalimumab followed by certolizumab pegol, 7 responded, 9 did not respond, 5 maintained remission, and 2 had insufficient records to evaluate the efficacy of certolizumab pegol.

None of the factors analyzed via multivariate analysis—age, gender, duration of CD, previous exposure to infiximab, duration of treatment with adalimumab and/or certolizumab pegol, body weight, or BMI—was found to be independently predictive of clinical response or remission. These results suggest that weight-based dosing of adalimumab and certolizumab pegol does not appear to be necessary.

## Neurologic Complications Associated with Tumor Necrosis Factor- $\alpha$ Antagonists Are Rare But Can Be Serious

While generally safe, anti-tumor necrosis factor (anti-TNF) agents have been associated with occasional reports of neurologic adverse events, including demyelination, peripheral neuropathy, optic neuritis, and Guillain-Barré syndrome (GBS). To verify these infrequent reports, Parakkal and colleagues conducted a review of neurologic adverse events collected via the US Food and Drug Administration's Adverse Event Reporting System (AERS), which is available for public access. In this study, which was presented at DDW 2011, reports from the AERS were searched to identify neurologic adverse reactions associated with anti-TNF biologic medications; data from January 1, 2000 through December 31, 2009 were included. Reports were searched for any neurologic adverse events associated with etanercept, infliximab, adalimumab, or certolizumab pegol.

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

Overall, the study identified 141 cases of peripheral neuropathy, 136 cases of demyelination, 71 cases of optic neuritis, 33 cases of GBS, 17 cases of leukoencephalopathy, 13 cases of transverse myelitis, 10 cases of chronic inflammatory demyelinating polyneuropathy, and 1 case of posterior reversible encephalopathy syndrome. In addition, this study identified 3 cases of progressive multifocal leukoencephalopathy. In patients who had received biologic agents for the treatment of inflammatory bowel disease, the most common adverse events were peripheral neuropathy (33 cases), demyelination (29 cases), and optic neuritis (13 cases).

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

## Ustekinumab May Be Effective for Moderate-to-Severe Crohn's Disease

In another study presented at DDW 2011, Sandborn and colleagues evaluated the safety and efficacy of ustekinumab, a human monoclonal antibody to interleukin (IL)-12 and IL-23. A total of 526 patients with moderate-to-severe CD who failed prior anti-TNF therapy were randomized to receive either IV placebo or IV ustekinumab (1 mg/kg, 3 mg/kg, or 6 mg/kg) at Week 0. Patients who received IV ustekinumab induction therapy and were either responders (those who achieved a decrease in Crohn's Disease Activity Index [CDAI] score  $\geq 100$  points) or nonresponders at Week 6 were then separately re-randomized at Week 8 to maintenance therapy with 90 mg ustekinumab or placebo. This maintenance therapy was administered subcutaneously at Weeks 8 and 16, and patients were followed through Week 22. For patients who showed a response to IV placebo, maintenance therapy consisted of subcutaneous placebo at Weeks 8 and 16; placebo nonresponders received subcutaneous ustekinumab at Week 8 (270 mg) and Week 16 (90 mg).

The primary study endpoint (a reduction in CDAI score  $\geq 100$  points from baseline at Week 6) was achieved by 39.7% of patients in the 6-mg/kg ustekinumab group and 23.5% of patients in the placebo group ( $P=.005$ ). This study found no significant differences in clinical remission at Week 6; however, the 6-mg/kg ustekinumab group showed improvement in rates of clinical response and clinical remission by Week 8. Compared to placebo, all doses of ustekinumab showed statistically significant changes at Week 6 in CDAI scores, C-reactive protein levels, fecal lactoferrin levels, fecal calprotectin levels, Inflammatory Bowel Disease Questionnaire scores, and 70-point decreases in CDAI scores.

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

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

# Presentations in Endoscopy

## Water Infusion Method Improves Success Rate for Unsedated Screening Colonoscopy

In another study from DDW 2011, Pohl and colleagues presented results of a randomized controlled trial that compared warm water infusion versus air insufflations for aiding colonoscopy insertion in unsedated patients. The investigators hypothesized that the water method would allow more patients to complete screening colonoscopy without sedation.

In this study, 100 patients who had agreed to on-demand sedation were randomly assigned to either the water method (50 patients) or the air method (50 patients). In the former group, minimal air insufflation was used during scope insertion; in the latter group, warm water (37° C) was used for colon distention. In both groups, sedation was provided on demand: Patients who reported a pain score of 2 on a scale of 0–10 (10=most severe) were asked if they wanted medication; if they did, they were given midazolam (2.5 mg) and pethidine (25 mg). Air was insufflated during withdrawal to aid inspection.

Overall, the water method was associated with a significant increase in the proportion of patients who completed their colonoscopy without sedation (78% vs 60%;  $P<.05$ ). Moreover, among patients who requested medication, those in the water group required less medication to reach the cecum compared to patients in the air group ( $P<.05$ ). Another benefit of the water method was a significant reduction in the mean number of instances of patients requiring abdominal compressions or a change in position (29 vs 1.8;  $P<.001$ ).

However, the water method was also associated with a greater risk of interference. Of the 20 failures in the air group, all were due to requested medication. In contrast, only 4 of the 12 failures in the water group were due to requested medication; the remaining 8 failures (16%) were due to solubilized stool remnants causing blurred vision. In these patients, insertion was completed with air insufflations. The air method was also associated with a shorter mean cecal intubation time compared to the water method (6.2 minutes vs 8.2 minutes;  $P<.05$ ). In summary, warm water infusion achieved a higher success rate for unsedated or minimally sedated screening colonoscopy, but this method also increased the risk of interference.

## Combined Sphincterotomy and Balloon Dilation Allows for Removal of Large Bile Duct Stones

In patients undergoing endoscopic retrograde cholangiopancreatography (ERCP), endoscopic sphincterotomy

plus balloon dilation (ESBD) may provide more complete sphincter ablation than standard endoscopic sphincterotomy (ES), thus allowing for retrieval of larger bile duct stones. In a randomized controlled trial presented at DDW 2011, Teoh and colleagues compared the efficacy and safety of ESBD versus ES in patients with large stones in the common bile duct.

Between September 2005 and 2010, this study enrolled 126 consecutive patients who were scheduled for ERCP and had bile duct stones in a dilated common bile duct ( $\geq 1.3$  cm in diameter). After biliary access was gained, patients were randomly assigned to receive ES (66 patients) or ESBD (60 patients). No significant differences in patient demographics were noted.

A total of 39 patients (31%) had previously undergone ES. The mean size of the largest common bile duct stone was 12.9 mm in the ES group and 12.5 mm in the ESBD group. Patients in the ESBD arm underwent limited sphincterotomy (measuring one third to one half the size of the papilla) followed by balloon dilation of the sphincter with a balloon that was 15 mm in diameter and 3 cm in length. Stones were retrieved using the Dormia basket or balloon catheter; a basket mechanical lithotripter (BML) was used to crush stones that could not be extracted through the papillary orifice.

ESBD and ES were associated with similar stone clearance rates at the index session, both for all stones (87% vs 91%) and for stones at least 1.5 cm in size (80% vs 85%). However, patients in the ESBD group were significantly less likely to require BML for stone extraction compared to patients in the ES group (28% vs 45%;  $P=.047$ ). In terms of safety, ESBD and ES had similar complication rates (20% vs 18%, respectively) and similar rates of postsphincterotomy bleeding (8% vs 11%, respectively). No procedure-related deaths occurred. Overall, the investigators concluded that ESBD allowed for the retrieval of large common bile duct stones and reduced the requirement for BML compared to standard ES without increasing procedure-related morbidity.

## Combined Endoluminal Therapy for Barrett Esophagus with High-Grade Dysplasia or Early Carcinoma Has a High Initial Success Rate

In another presentation from DDW 2011, Guarner-Argente and colleagues presented a retrospective analysis of long-term outcomes in patients with BE and HGD or early cancer who received endoluminal therapy that aimed to completely eradicate all intestinal metaplasia. This

analysis included 165 patients, all of whom met the study's inclusion criteria and were followed for at least 1 year after the initiation of endoluminal therapy. The median patient age was 68 years, 84% of patients were male, the mean BE length was 3.4 cm, and nodular lesions were present in 53% of patients. The most common initial treatment was endoscopic resection (73%), followed by photodynamic therapy (16%), radiofrequency ablation (9%), or argon-plasma coagulation (2%). More than half of patients (55%) required multimodal therapy, which included wide-area endoscopic resection (50%), radiofrequency ablation (38%), focal endoscopic resection (33%), argon-plasma coagulation (32%), and photodynamic therapy (22%).

Of the 165 patients with at least 1 year of follow-up data (median follow-up period, 41 months), 156 patients (95%) attained complete eradication of neoplasia, and 136 patients (82%) attained complete eradication of all intestinal metaplasia. The latter endpoint was attained after an average of 5 months (range, 0–43 months) and 2 sessions (range, 2–10). Reasons for lack of success included failure to clear intestinal metaplasia (11.5%), failure to clear early cancer (4.9%), and treatment withdrawal (1.2%).

Recurrences occurred in 40% of patients during the follow-up period. Among the patients who attained complete eradication of all intestinal metaplasia, 33% of patients developed recurrent intestinal metaplasia, and 8% of patients developed recurrent dysplasia. Among patients who attained complete eradication of neoplasia, recurrent dysplasia occurred in 32% of patients. However, re-treatment was effective in 90% of cases. In terms of adverse events, 24% of patients developed complications, 12% of patients developed stenosis, and there was 1 treatment-related death (which occurred 2 weeks after photodynamic therapy).

Overall, the researchers concluded that combined endoluminal therapy aiming for complete eradication of all intestinal metaplasia was associated with a high initial success rate. However, recurrent intestinal metaplasia and dysplasia were common, highlighting the need for continued surveillance.

### Stents Can Provide Long-Term Dysphagia Relief for Some Patients with Refractory Benign Esophageal Strictures

In a study presented by Van Boeckel and colleagues at DDW 2011, temporary self-expanding plastic stents (SEPS) were compared to biodegradable stents for the treatment of refractory benign esophageal strictures (RBES). This study enrolled 38 patients with RBES-related dysphagia who were divided into 2 consecutive groups: 1 group (20 patients) received SEPS, to be removed after 6 weeks; the other group (18 patients) received biodegradable stents. There was no significant difference between groups in terms of the causes of the strictures.

Stent placement success rates were similar in both groups: 95% for SEPS versus 89% for biodegradable stents. In the 19 patients who received SEPS, the stents were subsequently removed in 16 patients (84%); SEPS were not removed in 3 patients (15%). In terms of clinical outcomes, 30% of patients in the SEPS group remained dysphagia-free over a median follow-up period of 385 days; in the biodegradable stent group, 33% of patients remained dysphagia-free over a median follow-up period of 166 days.

Recurrent dysphagia developed in 50% of patients in the SEPS group and 67% of patients in the biodegradable stent group. The incidence of major complications was similar for SEPS and biodegradable stents (10% vs 22%, respectively). Major complications in the SEPS group included hemorrhage and perforation in 1 patient each; major complications in the biodegradable stent group included hemorrhage and severe retrosternal pain in 2 patients each. However, a significant difference between the 2 groups was the lower mean number of reinterventions in the biodegradable stent group compared to the SEPS group (0.8 vs 1.3;  $P=.03$ ).

### Preliminary Results Suggest That Adjustable Intra-gastric Balloons May Be Effective for Weight Loss Management

Potential advantages of using an adjustable balloon for weight loss management include improved comfort, greater efficacy, and the ability for prolonged implantation due to the inclusion of a migration prevention anchor. The adjustable balloon can also be removed using a polypectomy snare. In a study presented at DDW 2011, Machytka and colleagues reported preliminary 12-month results for the first adjustable intra-gastric balloons implanted for weight loss management.

This study enrolled 18 patients (15 females) with a mean BMI of 39.4 kg/m<sup>2</sup> (range, 29.4–53.2 kg/m<sup>2</sup>) and a mean weight of 114.9 kg (range, 73.5–163 kg). Implantation was performed transorally under conscious sedation. Balloons were filled with saline; the average volume of saline was 406.9 cc (range, 350–600 cc).

After 24 weeks, patients had lost an average of 15.6 kg (26.4% excess weight loss); after 52 weeks, the mean weight loss was 35.5 kg (67.3% excess weight loss). Adjustments were successfully performed in 16 patients, including 6 downward adjustments to improve tolerability and 10 upward adjustments due to weight loss plateaus. These adjustments resulted in additional mean weight losses of 4.6 kg and 8.1 kg, respectively. There were no major complications; nonetheless, balloons were removed in 7 of 18 patients.

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**References:** 1. DiPalma JA, Rodriguez R, McGowan CE, et al. A Randomized Clinical Study Evaluating the Safety and Efficacy of a new, reduced-volume, oral sulfate colon-cleansing preparation for colonoscopy. *Am J Gastroenterol.* 2009;104:2275-2284. 2. SUPREP Bowel Prep Kit [package insert]. Braintree, MA: Braintree Laboratories, Inc; 2010.

## SUPREP P/I SEPT PG 580

**BRIEF SUMMARY:** Before prescribing, please see full Prescribing Information and Medication Guide for SUPREP® Bowel Prep Kit. **INDICATIONS AND USAGE:** An osmotic laxative indicated for cleansing of the colon as a preparation for colonoscopy in adults. **CONTRAINDICATIONS:** Use is contraindicated in the following conditions: gastrointestinal (GI) obstruction, bowel perforation, toxic colitis and toxic megacolon, gastric retention, ileus, known allergies to components of the kit. **WARNINGS AND PRECAUTIONS:** SUPREP Bowel Prep Kit is an osmotic laxative indicated for cleansing of the colon as a preparation for colonoscopy in adults. Use is contraindicated in the following conditions: gastrointestinal (GI) obstruction, bowel perforation, toxic colitis and toxic megacolon, gastric retention, ileus, known allergies to components of the kit. Use caution when prescribing for patients with a history of seizures, arrhythmias, impaired gag reflex, regurgitation or aspiration, severe active ulcerative colitis, impaired renal function or patients taking medications that may affect renal function or electrolytes. Pre-dose and post-colonoscopy ECG's should be considered in patients at increased risk of serious cardiac arrhythmias. Use can cause temporary elevations in uric acid. Uric acid fluctuations in patients with gout may precipitate an acute flare. Administration of osmotic laxative products may produce mucosal aphthous ulcerations, and there have been reports of more serious cases of ischemic colitis requiring hospitalization. Patients with impaired water handling who experience severe vomiting should be closely monitored including measurement of electrolytes. Advise all patients to hydrate adequately before, during, and after use. Each bottle must be diluted with water to a final volume of 16 ounces and ingestion of additional water as recommended is important to patient tolerance. **Pregnancy:** Pregnancy Category C. Animal reproduction studies have not been conducted. It is not known whether this product can cause fetal harm or can affect reproductive capacity. **Pediatric Use:** Safety and effectiveness in pediatric patients has not been established. **Geriatric Use:** Of the 375 patients who took SUPREP Bowel Prep Kit in clinical trials, 94 (25%) were 65 years of age or older, while 25 (7%) were 75 years of age or older. No overall differences in safety or effectiveness of SUPREP Bowel Prep Kit administered as a split-dose (2-day) regimen were observed between geriatric patients and younger patients. **DRUG INTERACTIONS:** Oral medication administered within one hour of the start of administration of SUPREP may not be absorbed completely. **ADVERSE REACTIONS:** Most common adverse reactions (>2%) are overall discomfort, abdominal distention, abdominal pain, nausea, vomiting and headache. **Oral Administration: Split-Dose (Two-Day) Regimen: Early in the evening prior to the colonoscopy:** Pour the contents of one bottle of SUPREP Bowel Prep Kit into the mixing container provided. Fill the container with water to the 16 ounce fill line, and drink the entire amount. Drink two additional containers filled to the 16 ounce line with water over the next hour. Consume only a light breakfast or have only clear liquids on the day before colonoscopy. **Day of Colonoscopy (10 to 12 hours after the evening dose):** Pour the contents of the second SUPREP Bowel Prep Kit into the mixing container provided. Fill the container with water to the 16 ounce fill line, and drink the entire amount. Drink two additional containers filled to the 16 ounce line with water over the next hour. Complete all SUPREP Bowel Prep Kit and required water at least one hour prior to colonoscopy. Consume only clear liquids until after the colonoscopy. **STORAGE:** Store at 20°-25°C (68°-77°F). Excursions permitted between 15°-30°C (59°-86°F). **Rx only.** Distributed by Braintree Laboratories, Inc. Braintree, MA 02185

**For additional information, please call 1-800-874-6756 or visit [www.suprekit.com](http://www.suprekit.com)**

# OUT WITH THE OLD IN WITH THE SU

## SUPREP The bowel prep, reinvented

- Effective bowel cleansing<sup>1,2</sup>
- No sodium phosphate
- Low volume
- ACG-recommended split-dose regimen

SUPREP P/U SEPT PG 579

FPO



### Important Safety Information

SUPREP<sup>®</sup> Bowel Prep Kit is an osmotic laxative indicated for cleansing of the colon as a preparation for colonoscopy in adults. Most common adverse reactions (>2%) are overall discomfort, abdominal distention, abdominal pain, nausea, vomiting and headache.

Use is contraindicated in the following conditions: gastrointestinal (GI) obstruction, bowel perforation, toxic colitis and toxic megacolon, gastric retention, ileus, known allergies to components of the kit. Use caution when prescribing for patients with a history of seizures, arrhythmias, impaired gag reflex, regurgitation or aspiration, severe active ulcerative colitis, impaired renal function or patients taking medications that may affect renal function or electrolytes. Use can cause temporary elevations in uric acid. Uric acid fluctuations in patients with gout may precipitate an acute flare. Administration of osmotic laxative products may produce mucosal aphthous ulcerations, and there have been reports of more serious cases of ischemic colitis requiring hospitalization. Patients with impaired water handling who experience severe vomiting should be closely monitored including measurement of electrolytes. Advise all patients to hydrate adequately before, during, and after use. Each bottle must be diluted with water to a final volume of 16 ounces and ingestion of additional water as recommended is important to patient tolerance.

*Please see brief summary of Prescribing Information on adjacent page.*

**SUPREP<sup>®</sup>**  
**BOWEL PREP KIT**  
(sodium sulfate, potassium  
sulfate and magnesium sulfate)  
Oral Solution

(17.5g/3.13g/1.6g) per 6 ounces