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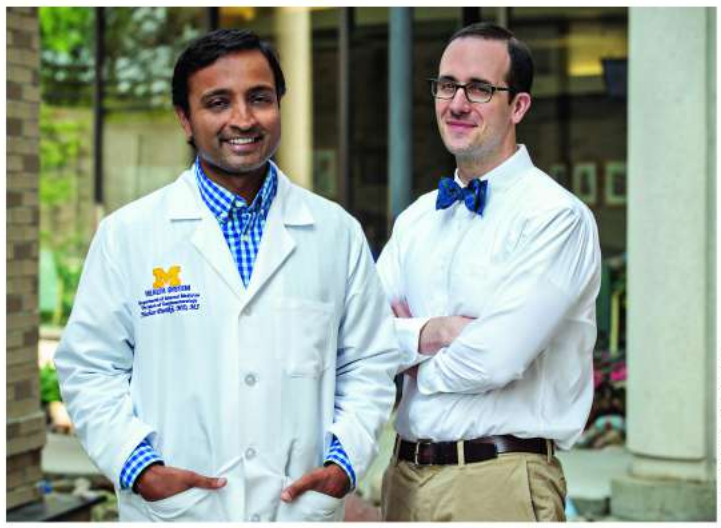

University of Michigan

Dr. Neehar D. Parikh (left) and Dr. Elliot B. Tapper reported an increase in deaths from liver cirrhosis and hepatocellular carcinoma from 1999 to 2016.

Deaths from liver disease surged in U.S. since 1999

BY MICHELE G. SULLIVAN
MDedge News

Deaths from cirrhosis of the liver in the United States increased by 65% during 1999-2016, while deaths from hepatocellular carcinoma more than doubled.

Cirrhosis mortality showed a sharp rise beginning in 2009, with a 3.6% annual increase driven entirely by a surge in alcoholic cirrhosis among young people aged 25-34 years, Elliot B. Tapper, MD, and Neehar D. Parikh, MD, reported in the BMJ. The uptick in hepatocellular carcinoma, however, was gradual and consistent, with a 2% annual increase felt mostly in older people, wrote Dr. Tapper and Dr. Parikh, both at the University of Michigan, Ann Arbor.

"The increasing mortality due to cirrhosis and hepatocellular carcinoma speaks to the expanding socioeconomic impact of liver disease," the colleagues wrote. "Adverse trends in liver-related mortality are particularly unfortunate given that in most cases the liver disease is preventable. Understanding the factors associated with mortality due to these conditions

See **Liver disease** · *page 19*

CMS proposal to level E/M payments raises concerns

BY GREGORY TWACHTMAN
MDedge News

Citing the need to reduce paperwork hassles, officials at the Centers for Medicare & Medicaid Services are proposing to flatten the payment for evaluation and management (E/M) visits coded at levels 2-5.

The CMS outlined how the proposal would affect payment using 2018 rates to model the change. The proposal would set the payment rate for level 1 E/M office visits for new patients at $44, down from the $45 using the current methodology. Levels 2-5 would receive $135. Currently, payments for level 2 visits are set at $76, level 3 at $110, level 4 at $167, and level 5 at $211.

For office visits with established patients, the proposed rate would be $24, up from the current payment of $22 for a level 1 visit. Levels 2-5 would receive $93. Under the current methodology, payments for level 2 visits are set at $45, level 3 at $74, level 4 at $109, and level 5 at $148.

The change also comes with a reduced documentation burden, so the same documentation is needed regardless of which level between 2 and 5 the office visit is, a move that is expected to save time.

The CMS outlined its vision for changes to the E/M payment in the proposed update to the 2019 Medicare physician fee schedule. Comments on the

See **CMS** · *page 6*

INSIDE

AGA Clinical Practice Update: Tumor seeding with endoscopic procedures

BY AMY KARON
MDedge News

Certain endoscopic procedures carry the risk of tumor seeding. In prior studies, these rates were 0.005%-0.009% for patients undergoing percutaneous abdominal biopsy, 1.6% for percutaneous radiofrequency ablation of hepatocellular carcinoma, and 2.7% for needle biopsy of hepatocellular carcinoma. When placing percutaneous endoscopic gastrostomy tubes, the "pull-through" technique is most common but "should

See **Seeding** · *page 23*

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MAVYRET: FOR CHRONIC HCV

TREAT ALL GENOTYPES IN AS FEW AS 8 WEEKS

THE ONLY 8-WEEK PANGENOTYPIC REGIMEN FOR GT 1-6 TREATMENT-NAÏVE, NON-CIRRHOTIC PATIENTS[1]

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION[1]

MAVYRET™ (glecaprevir and pibrentasvir) tablets are indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A). MAVYRET is also indicated for the treatment of adult patients with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor (PI), but not both.

IMPORTANT SAFETY INFORMATION[1]

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV: Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with MAVYRET. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct-acting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

CONTRAINDICATIONS

MAVYRET is contraindicated:

- In patients with severe hepatic impairment (Child-Pugh C)
- With the following drugs: atazanavir or rifampin

WARNINGS AND PRECAUTIONS

Risk of Reduced Therapeutic Effect Due to Concomitant Use of MAVYRET with Carbamazepine, Efavirenz-containing Regimens, or St. John's Wort

- Carbamazepine, efavirenz, and St. John's Wort may significantly decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect of MAVYRET. The use of these agents with MAVYRET is not recommended.

ADVERSE REACTIONS

Most common adverse reactions observed with MAVYRET:

- >10% of subjects: headache and fatigue
- ≥5% of subjects: headache, fatigue, and nausea

abbvie

 46A-1941903 April 2018 Printed in U.S.A.

THE ONLY 8-WEEK PANGENOTYPIC REGIMEN. HIGH CURE* RATES IN CLINICAL TRIALS[1]

98%

CURE* RATE (SVR12)

across 3 studies in GT 1-6 TN and GT 1, 2, 4-6 PRS-experienced,† NC patients who received 8 weeks of treatment (n=745/763).

SVR12 range: 93-100% (ITT); 96-100% (mITT).

- **NO** baseline viral load restrictions
- **NO** dose adjustment for renal impairment
- **NO** baseline resistance testing required
- **NO** ribavirin

*Cure = Sustained virologic response (SVR12); HCV RNA <LLOQ 12 weeks after the end of treatment.

†PRS-experienced = Prior treatment experience with regimens containing IFN, pegIFN, RBV, and/or SOF, but no prior treatment experience with an HCV NS3/4A protease inhibitor or NS5A inhibitor.

GT = Genotype; HCV = Hepatitis C virus; IFN = Interferon; ITT = Intention to treat; LLOQ = Lower limit of quantification; mITT = ITT population modified to exclude patients who did not achieve SVR12 for reasons other than virologic failure; NC = Non-cirrhotic; pegIFN = Pegylated interferon; RBV = Ribavirin; SOF = Sofosbuvir; TN = Treatment-naïve.

Study Designs

SURVEYOR-2, Parts 2 and 4[1-4]: A randomized, open-label, multicenter, 4-part, phase 2 study to evaluate the efficacy, safety, and pharmacokinetics of MAVYRET with or without RBV in 691 TN or treatment-experienced (ie, IFN or pegIFN ± RBV, or SOF + RBV ± pegIFN) GT 2-6–infected adults, without cirrhosis or with compensated cirrhosis. Part 2: GT 2, 3 NC patients were administered MAVYRET for 8 weeks and GT 3 patients without cirrhosis or with compensated cirrhosis were administered MAVYRET with or without RBV for 12 weeks. Part 4: GT 2, 4-6 NC patients were administered MAVYRET for 8 weeks. Primary endpoints: SVR12 in each treatment arm and noninferiority of SVR12 for GT 2 (Part 4) to historical control with 12 weeks of SOF + RBV.

ENDURANCE-1[1,5]: A randomized, open-label, multicenter, phase 3 study to evaluate the efficacy and safety of MAVYRET for 8 or 12 weeks in 703 TN or prior treatment–experienced (ie, IFN or pegIFN ± RBV, or SOF + RBV ± pegIFN) GT 1-infected adults without cirrhosis and with or without HIV-1 co-infection. Primary endpoints: SVR12 in the 12-week ITT-PS population (ITT population excluding patients with HIV co-infection and patients with SOF experience); SVR12 in the 8-week arm compared with the 12-week arm in the ITT-PS and per-protocol ITT-PS populations ("per-protocol" excludes patients with premature discontinuation or virologic failure prior to week 8 and missing data in the SVR12 window).

ENDURANCE-3[1,5]: A partially randomized, open-label, active-controlled, multicenter, phase 3 study to evaluate the efficacy and safety of MAVYRET for 8 or 12 weeks vs SOF + daclatasvir (DCV) for 12 weeks in 505 TN GT 3-infected adults without cirrhosis. Primary endpoints: Demonstrate noninferiority in the percentage of patients achieving SVR12 with 12 weeks of MAVYRET treatment to 12 weeks of treatment with SOF + DCV, and demonstrate noninferiority of 8 weeks of MAVYRET treatment to 12 weeks of MAVYRET treatment.

References: 1. MAVYRET [package insert]. North Chicago, IL: AbbVie Inc.; 2017. **2.** Data on file. ABVRRTI64729. AbbVie Inc.; 2017. **3.** Kwo PY, Wyles DL, Wang S, et al. 100% SVR12 with ABT-493 + ABT-530 with or without ribavirin in treatment-naïve HCV genotype 3-infected patients with cirrhosis. Poster presented at: 51st Annual Meeting of the European Association for the Study of the Liver; April 16, 2016; Barcelona, Spain. **4.** Hassanein T, Wyles D, Wang S, et al. SURVEYOR-II, Part 4: glecaprevir/pibrentasvir demonstrates high SVR rates in patients with HCV genotype 2, 4, 5, or 6 infection without cirrhosis following an 8-week treatment duration. Poster presented at: 67th Annual Meeting of the American Association for the Study of Liver Diseases; November 11-15, 2016; Boston, MA. **5.** Zeuzem S, Foster GR, Wang S, et al. Glecaprevir-pibrentasvir for 8 or 12 weeks in HCV genotype 1 or 3 infection. *N Engl J Med.* 2018;378(4):354-369.

Please see adjacent page for a brief summary of the full Prescribing Information.

MAVYRET™
glecaprevir/pibrentasvir
100 mg/40 mg tablets

MAVYRET™ (glecaprevir and pibrentasvir) tablets, for oral use

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV

Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with MAVYRET. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct-acting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

MAVYRET is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A). MAVYRET is also indicated for the treatment of adult patients with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor (PI), but not both.

CONTRAINDICATIONS

MAVYRET is contraindicated in patients with severe hepatic impairment (Child-Pugh C) *[see Use in Specific Populations]*.

MAVYRET is contraindicated with atazanavir or rifampin *[see Drug Interaction]*.

WARNINGS AND PRECAUTIONS

Risk of Hepatitis B Virus Reactivation in Patients Coinfected with HCV and HBV

Hepatitis B virus (HBV) reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct-acting antivirals, and who were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure and death. Cases have been reported in patients who are HBsAg positive and also in patients with serologic evidence of resolved HBV infection (i.e., HBsAg negative and anti-HBc positive). HBV reactivation has also been reported in patients receiving certain immunosuppressant or chemotherapeutic agents; the risk of HBV reactivation associated with treatment with HCV direct-acting antivirals may be increased in these patients.

HBV reactivation is characterized as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level. In patients with resolved HBV infection reappearance of HBsAg can occur. Reactivation of HBV replication may be accompanied by hepatitis, i.e., increase in aminotransferase levels and, in severe cases, increases in bilirubin levels, liver failure, and death can occur.

Test all patients for evidence of current or prior HBV infection by measuring HBsAg and anti- HBc before initiating HCV treatment with MAVYRET. In patients with serologic evidence of HBV infection, monitor for clinical and laboratory signs of hepatitis flare or HBV reactivation during HCV treatment with MAVYRET and during post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

Risk of Reduced Therapeutic Effect Due to Concomitant Use of MAVYRET with Carbamazepine, Efavirenz Containing Regimens, or St. John's Wort

Carbamazepine, efavirenz, and St. John's wort may significantly decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect of MAVYRET. The use of these agents with MAVYRET is not recommended.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of MAVYRET cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Overall Adverse Reactions in HCV-Infected Adults Without Cirrhosis or With Compensated Cirrhosis (Child-Pugh A)

The adverse reactions data for MAVYRET in subjects without cirrhosis or with compensated cirrhosis (Child-Pugh A) were derived from nine Phase 2 and 3 trials which evaluated approximately 2,300 subjects infected with genotype 1, 2, 3, 4, 5, or 6 HCV who received MAVYRET for 8, 12 or 16 weeks.

The overall proportion of subjects who permanently discontinued treatment due to adverse reactions was 0.1% for subjects who received MAVYRET for 8, 12 or 16 weeks.

The most common adverse reactions, all grades, observed in greater than or equal to 5% of subjects receiving 8, 12, or 16 weeks of treatment with MAVYRET were headache (13%), fatigue (11%), and nausea (8%). In subjects receiving MAVYRET who experienced adverse reactions, 80% had an adverse reaction of mild severity (Grade 1). One subject experienced a serious adverse reaction.

Adverse reactions (type and severity) were similar for subjects receiving MAVYRET for 8, 12 or 16 weeks. The type and severity of adverse reactions in subjects with compensated cirrhosis (Child-Pugh A) were comparable to those seen in subjects without cirrhosis.

Adverse Reactions in HCV-Infected Adults treated with MAVYRET in Controlled Trials

ENDURANCE-2

Among 302 treatment-naïve or PRS treatment-experienced, HCV genotype 2 infected adults enrolled in ENDURANCE-2, adverse reactions (all intensity) occurring in at least 5% of subjects treated with MAVYRET for 12 weeks are presented in Table 1. In subjects treated with MAVYRET for 12 weeks, 32% reported an adverse reaction, of which 98% had adverse reactions of mild or moderate severity. No subjects treated with MAVYRET or placebo in ENDURANCE-2 permanently discontinued treatment due to an adverse drug reaction.

Table 1. Adverse Reactions Reported in ≥5% of Treatment-Naïve and PRS-Experienced Adults Without Cirrhosis Receiving MAVYRET for 12 Weeks in ENDURANCE-2

Adverse Reaction	MAVYRET 12 Weeks (N = 202) %	Placebo 12 Weeks (N = 100) %
Headache	9	6
Nausea	6	2
Diarrhea	5	2

ENDURANCE-3

Among 505 treatment-naïve, HCV genotype 3 infected adults without cirrhosis enrolled in ENDURANCE-3, adverse reactions (all intensity) occurring in at least 5% of subjects treated with MAVYRET for 8 or 12 weeks are presented in Table 2. In subjects treated with MAVYRET, 45% reported an adverse reaction, of which 99% had adverse reactions of mild or moderate severity. The proportion of subjects who permanently discontinued treatment due to adverse reactions was 0%, < 1% and 1% for the MAVYRET 8 week arm, MAVYRET 12 week arm and DCV + SOF arm, respectively.

Table 2. Adverse Reactions Reported in ≥5% of Treatment-Naïve Adults Without Cirrhosis Receiving MAVYRET for 8 Weeks or 12 Weeks in ENDURANCE-3

Adverse Reaction	MAVYRET* 8 Weeks (N = 157) %	MAVYRET 12 Weeks (N = 233) %	DCV[1] + SOF[2] 12 Weeks (N = 115) %
Headache	16	17	15
Fatigue	11	14	12
Nausea	9	12	12
Diarrhea	7	3	3

[1] DCV=daclatasvir
[2] SOF=sofosbuvir
* The 8 week arm was a non-randomized treatment arm.

Adverse Reactions in HCV-Infected Adults with Severe Renal Impairment Including Subjects on Dialysis

The safety of MAVYRET in subjects with chronic kidney disease (Stage 4 or Stage 5 including subjects on dialysis) with genotypes 1, 2, 3, 4, 5 or 6 chronic HCV infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) was assessed in 104 subjects (EXPEDITION-4) who received MAVYRET for 12 weeks. The most common adverse reactions observed in greater than or equal to 5% of subjects receiving 12 weeks of treatment with MAVYRET were pruritus (17%), fatigue (12%), nausea (9%), asthenia (7%), and headache (6%). In subjects treated with MAVYRET who reported an adverse reaction, 90% had adverse reactions of mild or moderate severity (Grade 1 or 2). The proportion of subjects who permanently discontinued treatment due to adverse reactions was 2%.

Laboratory Abnormalities

Serum bilirubin elevations

Elevations of total bilirubin at least 2 times the upper limit of normal occurred in 3.5% of subjects treated with MAVYRET versus 0% in placebo; these elevations were observed in 1.2% of subjects across the Phase 2 and 3 trials. MAVYRET inhibits OATP1B1/3 and is a weak inhibitor of UGT1A1 and may have the potential to impact bilirubin transport and metabolism, including direct and indirect bilirubin. No subjects experienced jaundice and total bilirubin levels decreased after completing MAVYRET.

DRUG INTERACTIONS

Mechanisms for the Potential Effect of MAVYRET on Other Drugs

Glecaprevir and pibrentasvir are inhibitors of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide (OATP) 1B1/3. Coadministration with MAVYRET may increase plasma concentration of drugs that are substrates of P-gp, BCRP, OATP1B1 or OATP1B3. Glecaprevir and pibrentasvir are weak inhibitors of cytochrome P450 (CYP) 3A, CYP1A2, and uridine glucuronosyltransferase (UGT) 1A1.

Fluctuations in INR values may occur in patients receiving warfarin concomitant with HCV treatment, including treatment with MAVYRET. If MAVYRET is coadministered with warfarin, close monitoring of INR values is recommended during treatment and post-treatment follow-up.

Mechanisms for the Potential Effect of Other Drugs on MAVYRET

Glecaprevir and pibrentasvir are substrates of P-gp and/or BCRP. Glecaprevir is a substrate of OATP1B1/3. Coadministration of MAVYRET with drugs that inhibit hepatic P-gp, BCRP, or OATP1B1/3 may increase the plasma concentrations of glecaprevir and/or pibrentasvir.

Coadministration of MAVYRET with drugs that induce P-gp/CYP3A may decrease glecaprevir and pibrentasvir plasma concentrations.

Carbamazepine, efavirenz, and St. John's wort may significantly decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect of MAVYRET. The use of these agents with MAVYRET is not recommended *[see Warnings and Precautions]*.

Established and Other Potential Drug Interactions

Table 3 provides the effect of MAVYRET on concentrations of coadministered drugs and the effect of coadministered drugs on glecaprevir and pibrentasvir *[see Contraindications]*.

Table 3. Potentially Significant Drug Interactions Identified in Drug Interaction Studies

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comments
Antiarrhythmics:		
Digoxin	↑ digoxin	Measure serum digoxin concentrations before initiating MAVYRET. Reduce digoxin concentrations by decreasing the dose by approximately 50% or by modifying the dosing frequency and continue monitoring.
Anticoagulants:		
Dabigatran etexilate	↑ dabigatran	If MAVYRET and dabigatran etexilate are coadministered, refer to the dabigatran etexilate prescribing information for dabigatran etexilate dose modifications in combination with P-gp inhibitors in the setting of renal impairment.
Anticonvulsants:		
Carbamazepine	↓ glecaprevir ↓ pibrentasvir	Coadministration may lead to reduced therapeutic effect of MAVYRET and is not recommended.
Antimycobacterials:		
Rifampin	↓ glecaprevir ↓ pibrentasvir	Coadministration is contraindicated because of potential loss of therapeutic effect *[see Contraindications]*.
Ethinyl Estradiol-Containing Products:		
Ethinyl estradiol-containing medications such as combined oral contraceptives	↔ glecaprevir ↔ pibrentasvir	Coadministration of MAVYRET may increase the risk of ALT elevations and is not recommended.
Herbal Products:		
St. John's wort (*hypericum perforatum*)	↓ glecaprevir ↓ pibrentasvir	Coadministration may lead to reduced therapeutic effect of MAVYRET and is not recommended.
HIV-Antiviral Agents:		
Atazanavir	↑ glecaprevir ↑ pibrentasvir	Coadministration is contraindicated due to increased risk of ALT elevations *[see Contraindications]*.
Darunavir Lopinavir Ritonavir	↑ glecaprevir ↑ pibrentasvir	Coadministration is not recommended.
Efavirenz	↓ glecaprevir ↓ pibrentasvir	Coadministration may lead to reduced therapeutic effect of MAVYRET and is not recommended.
HMG-CoA Reductase Inhibitors:		
Atorvastatin Lovastatin Simvastatin	↑ atorvastatin ↑ lovastatin ↑ simvastatin	Coadministration may increase the concentration of atorvastatin, lovastatin, and simvastatin. Increased statin concentrations may increase the risk of myopathy, including rhabdomyolysis. Coadministration with these statins is not recommended.
Pravastatin	↑ pravastatin	Coadministration may increase the concentration of pravastatin. Increased statin concentrations may increase the risk of myopathy, including rhabdomyolysis. Reduce pravastatin dose by 50% when coadministered with MAVYRET.
Rosuvastatin	↑ rosuvastatin	Coadministration may significantly increase the concentration of rosuvastatin. Increased statin concentrations may increase the risk of myopathy, including rhabdomyolysis. Rosuvastatin may be administered with MAVYRET at a dose that does not exceed 10 mg.
Fluvastatin Pitavastatin	↑ fluvastatin ↑ pitavastatin	Coadministration may increase the concentrations of fluvastatin and pitavastatin. Increased statin concentrations may increase the risk of myopathy, including rhabdomyolysis. Use the lowest approved dose of fluvastatin or pitavastatin. If higher doses are needed, use the lowest necessary statin dose based on a risk/benefit assessment.
Immunosuppressants:		
Cyclosporine	↑ glecaprevir ↑ pibrentasvir	MAVYRET is not recommended for use in patients requiring stable cyclosporine doses > 100 mg per day.

↑= increase; ↓= decrease; ↔ = no effect

Drugs with No Observed Clinically Significant Interactions with MAVYRET

No dose adjustment is required when MAVYRET is coadministered with the following medications: abacavir, amlodipine, buprenorphine, caffeine, dextromethorphan, dolutegravir, elvitegravir/cobicistat, emtricitabine, felodipine, lamivudine, lamotrigine, losartan, methadone, midazolam, naloxone, norethindrone or other progestin-only contraceptives, omeprazole, raltegravir, rilpivirine, sofosbuvir, tacrolimus, tenofovir alafenamide, tenofovir disoproxil fumarate, tolbutamide, and valsartan.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

No adequate human data are available to establish whether or not MAVYRET poses a risk to pregnancy outcomes. In animal reproduction studies, no adverse developmental effects were observed when the components of MAVYRET were administered separately during organogenesis at exposures up to 53 times (rats; glecaprevir) or 51 and 1.5 times (mice and rabbits, respectively; pibrentasvir) the human exposures at the recommended dose of MAVYRET *[see Data]*. No definitive conclusions regarding potential developmental effects of glecaprevir could be made in rabbits, since the highest achieved glecaprevir exposure in this species was only 7% (0.07 times) of the human exposure at the recommended dose. There were no effects with either compound in rodent pre/post-natal developmental studies in which maternal systemic exposures (AUC) to glecaprevir and pibrentasvir were approximately 47 and 74 times, respectively, the exposure in humans at the recommended dose *[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Glecaprevir

Glecaprevir was administered orally to pregnant rats (up to 120 mg/kg/day) and rabbits (up to 60 mg/kg/day) during the period of organogenesis (gestation days (GD) 6 to 18, and GD 7 to 19, respectively). No adverse embryo-fetal effects were observed in rats at dose levels up to 120 mg/kg/day (53 times the exposures in humans at the recommended human dose (RHD)). In rabbits, the highest glecaprevir exposure achieved was 7% (0.07 times) of the exposure in humans at RHD. As such, data in rabbits during organogenesis are not available for glecaprevir systemic exposures at or above the exposures in humans at the RHD.

In the pre/post-natal developmental study in rats, glecaprevir was administered orally (up to 120 mg/kg/day) from GD 6 to lactation day 20. No effects were observed at maternal exposures 47 times the exposures in humans at the RHD.

Pibrentasvir

Pibrentasvir was administered orally to pregnant mice and rabbits (up to 100 mg/kg/day) during the period of organogenesis (GD 6 to 15, and GD 7 to 19, respectively). No adverse embryo-fetal effects were observed at any studied dose level in either species. The systemic exposures at the highest doses were 51 times (mice) and 1.5 times (rabbits) the exposures in humans at the RHD.

In the pre/post-natal developmental study in mice, pibrentasvir was administered orally (up to 100 mg/kg/day) from GD 6 to lactation day 20. No effects were observed at maternal exposures approximately 74 times the exposures in humans at the RHD.

Lactation

Risk Summary

It is not known whether the components of MAVYRET are excreted in human breast milk, affect human milk production, or have effects on the breastfed infant. When administered to lactating rodents, the components of MAVYRET were present in milk, without effect on growth and development observed in the nursing pups *[see Data]*.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MAVYRET and any potential adverse effects on the breastfed child from MAVYRET or from the underlying maternal condition.

Data

No significant effects of glecaprevir or pibrentasvir on growth and post-natal development were observed in nursing pups at the highest doses tested (120 mg/kg/day for glecaprevir and 100 mg/kg/day for pibrentasvir). Maternal systemic exposure (AUC) to glecaprevir and pibrentasvir was approximately 47 or 74 times the exposure in humans at the RHD. Systemic exposure in nursing pups on post-natal day 14 was approximately 0.6 to 2.2 % of the maternal exposure for glecaprevir and approximately one quarter to one third of the maternal exposure for pibrentasvir.

Glecaprevir or pibrentasvir was administered (single dose; 5 mg/kg oral) to lactating rats, 8 to 12 days post parturition. Glecaprevir in milk was 13 times lower than in plasma and pibrentasvir in milk was 1.5 times higher than in plasma. Parent drug (glecaprevir or pibrentasvir) represented the majority (>96%) of the total drug-related material in milk.

Pediatric Use

Safety and effectiveness of MAVYRET in children less than 18 years of age have not been established.

Geriatric Use

In clinical trials of MAVYRET, 328 subjects were age 65 years and over (14% of the total number of subjects in the Phase 2 and 3 clinical trials) and 47 subjects were age 75 and over (2%). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects. No dosage adjustment of MAVYRET is warranted in geriatric patients.

Renal Impairment

No dosage adjustment of MAVYRET is required in patients with mild, moderate or severe renal impairment, including those on dialysis.

Hepatic Impairment

No dosage adjustment of MAVYRET is required in patients with mild hepatic impairment (Child-Pugh A). MAVYRET is not recommended in patients with moderate hepatic impairment (Child-Pugh B). Safety and efficacy have not been established in HCV-infected patients with moderate hepatic impairment. MAVYRET is contraindicated in patients with severe hepatic impairment (Child-Pugh C) due to higher exposures of glecaprevir and pibrentasvir *[see Contraindications]*.

OVERDOSAGE

In case of overdose, the patient should be monitored for any signs and symptoms of toxicities. Appropriate symptomatic treatment should be instituted immediately. Glecaprevir and pibrentasvir are not significantly removed by hemodialysis.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Risk of Hepatitis B Virus Reactivation in Patients Coinfected with HCV and HBV

Inform patients that HBV reactivation can occur in patients coinfected with HBV during or after treatment of HCV infection. Advise patients to tell their healthcare provider if they have a history of hepatitis B virus infection *[see Warnings and Precautions]*.

Drug Interactions

Inform patients that MAVYRET may interact with some drugs; therefore, patients should be advised to report to their healthcare provider the use of any prescription, non-prescription medication or herbal products *[see Contraindications, Warnings and Precautions and Drug Interactions]*.

Administration

Advise patients to take MAVYRET recommended dosage (three tablets) once daily with food as directed. Inform patients that it is important not to miss or skip doses and to take MAVYRET for the duration that is recommended by the physician.

If a dose is missed and it is:

- Less than 18 hours from the usual time that MAVYRET should have been taken – advise the patient to take the dose as soon as possible and then to take the next dose at the usual time.
- More than 18 hours from the usual time that MAVYRET should have been taken – advise the patient not to take the missed dose and to take the next dose at the usual time.

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LETTER FROM THE EDITOR: Summer is over, more health care changes are afoot


DR. ALLEN

CMS has released its proposed rule (see related articles and a commentary) and included changes as substantial as I have seen in the last two decades. Additionally, the Affordable Care Act has been under continued attack despite its majority support from our citizenry. Loss of the individual mandate, allowance of "skinny" health plans, a rewrite of association plan rules, elimination of cost-sharing reductions and premium support – all have contributed to a shifting away from socialized medical costs and toward a system of individual responsibility for health. Depending on one's political philosophy (and income), that may be bad or good.

Our article list this month will be interesting to many. The AGA produced a Clinical Practice Update about tumor seeding with endoscopic procedures. This should give us pause and make us reconsider our endoscopic practices. My wife (an endoscopy nurse in Minneapolis) has been asking for years whether pulling a PEG tube past an esophageal cancer might cause tumor seeding, and physicians have reassured her that there is no cause for worry. Turns out she was right (as usual). Deaths from liver disease in the U.S. have seen a dramatic increase since 1999, driven substantially by increasing alcohol use. Fecal transplants in irritable bowel syndrome? Possibly helpful, as reported in an article from Digestive Disease Week.®

As summer comes to an end, we head in to a tumultuous fall that will be dominated by November elections.

John I. Allen, MD, MBA, AGAF
Editor in Chief

CMS proposes site-neutral payments for hospital outpatient settings

BY GREGORY TWACHTMAN
MDedge News

Certain procedures conducted in the hospital outpatient setting could see a reimbursement cut under the physician fee schedule if a proposal introduced by the Centers for Medicare & Medicaid Services is finalized.

In the proposed update to the Outpatient Prospective Payment System (OPPS) and Ambulatory Surgical Center (ASC) Payment System for 2019, CMS is proposing to apply a physician fee schedule–equivalent for the clinic visit service when provided at an off-campus, provider-based department that is paid under OPPS.

According to CMS, the average current clinical visit paid by CMS is $116 with $23 being the average copay by the patient. If the proposal is finalized, the payment would drop to about $46 with an average patient copay of $9.

"This is intended to address concerns about recent consolidations in the market that reduce competition," CMS Administrator Seema Verma said during a July 25 press conference.

The American Hospital Association already is pushing back on this proposal.

"With today's proposed rule, CMS has once again showed a lack of understanding about the reality in which hospitals and health systems operate daily to serve the needs of their communities," AHA Executive Vice President Tom Nickels said in a statement. "In 2015, Congress clearly intended to provide current off-campus hospital clinics with the existing outpatient payment rate

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in recognition of the critical role they play in their communities. But CMS's proposal runs counter to this and will instead impede access to care for the most vulnerable patients."

The OPPS/ASC update also includes proposals to expand the list of covered surgical procedures that can be performed in an ASC, a move that Ms. Verma said would "provide patients with more choices and options for lower-priced care."

"For CY 2019, CMS is proposing to allow certain CPT codes outside of the surgical code range that directly crosswalk or are clinically similar to procedures within the CPT surgical code range to be included on the [covered procedure list] and is proposing to add certain cardiovascular codes to the ASC [covered procedure list] as a result," the CMS fact sheet notes.

Another change proposed by CMS relates to how ASC reimbursement rates are updated. They have been based on the consumer price index-urban, which has resulted in a decline in ASC payments relative to hospitals for the same service. For 2019-2023, CMS proposes to use the hopital market basket instead, which will help promote site neutrality between hospitals and ASCs. The AGA applauds this proposal, and has been working for it with the ACG and ASGE for nearly a decade.

In addition, the OPPS is seeking feedback on a number of topics.

One is related to price transparency. The agency is asking "whether providers and suppliers can and should be required to inform patients about charges and payment information for healthcare services and out-of-pocket costs, what data elements the public would find most useful, and what other charges are needed to empower patients," according to the fact sheet.

Finally, the agency is seeking more information on solutions to better promote interoperability.

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PERSPECTIVE

Proposed changes are drastic and sweeping

On July 12, 2018, CMS published a set of "proposed rules" that will have substantial impact on your practice. CMS released a 665-page document with 26 proposed changes in Medicare. A public comment period is open until Sept. 10, 2018. Final rules will be published in the fall with implementation expected in January 2019.

Medicare proposes to reduce the number of E/M coding levels to two (from five: these relate to current CPT codes 99201-99205 and 99211-99215), with documentation requirements reduced to those required for current level 2. If you tend to bill levels 4-5, your bottom line will be affected.

CMS wants to eliminate site-of-service differences in both clinic and ASC payments. This will modify the financial advantages gained by practices who sold their centers to hospital systems and for health systems that have HOPD endoscopy centers and clinics.

Endoscopy with biopsy and colonoscopy with polypectomy were again identified as being potentially overvalued and thus may trigger a re-analysis.

A policy change announced recently by CMS would allow Medicare Advantage plans to establish sequence requirements (step therapy) for medical therapies, including biologics.

While community practices clearly will be affected by these changes, the financial pressures on academic medical centers will be immense. AMC's have high fixed costs and deteriorating clinical margins. Clinical revenue supports not only clinical enterprises (including faculty sal-

Continued on page 8

Docs push back on step therapy in Medicare Advantage

BY GREGORY TWACHTMAN
MDedge News

A new policy that allows Medicare Advantage plans to use step therapy to control spending on prescription drug administered in the office is not going over well with doctors.

The Centers for Medicare & Medicaid Services announced the policy change Aug. 7, which will give Medicare Advantage plan sponsors the "choice of implementing step therapy to manage Part B drugs, beginning Jan. 1, 2019," the agency said in a statement.

The action is part of the broader Trump administration initiative to lower the prices and out-of-pocket costs of prescription drugs as outlined in the American Patients First blueprint.

By "implementing step therapy along with care coordination and drug adherence programs in [Medicare Advantage], it will lower costs and improve the quality of care for Medicare beneficiaries," CMS officials said in a statement. The move to allow step therapy will give Medicare Advantage plan sponsors the ability to negotiate the designation of a preferred drug, something the agency believes could result in lower prices for these drugs, which in turn will lower the copays for Medicare beneficiaries.

Plan sponsors will be required to pass savings onto beneficiaries through some sort of rewards program, according to a memo detailing the policy change, which also notes that plan rewards "cannot be offered in the form of cash or monetary rebate, but may be offered as gift cards or other items value to all eligible enrollees."

The value of the rewards must be more than half of the savings generated from implementing the step therapy program, according to the memo.

CMS officials noted that there will be a process that beneficiaries can follow if they believe they need direct access to a drug that would otherwise be available only after failing on another drug.

The American Gastroenterological Association "is concerned that the proposal could limit access for current and future beneficiaries and could add to the growing regulatory burden that physicians already face," according to a statement. AGA stated that "any change in policy must ensure that patients have access to the appropriate therapies to manage their diseases and not contribute to additional administrative burdens for physician practices." In addition to responding to CMS, AGA continues to advocate to Congress for patient protections for those subject to step therapy protocols in employer-sponsored health plans; learn more at http:/ow.ly/kp8l30lnDmp.

The new policy applies to only new prescriptions or administrations of Part B drugs. Patients will not have current treatments disrupted if that drug is not the first drug on the step therapy ladder. Additionally, patients will have the opportunity to make a one-time change in plans during the first quarter annually if they are finding the plan is not working for them. Plan sponsors must disclose that Part B drugs may be subject to step therapy.

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Less documentation time, less pay?

CMS *from page 1*

proposal are due Sept. 10, 2018.

The agency estimated that for most specialties, there would be minimal effect on this proposed change. However, for 10 specialties, payment reductions could result from this change. The proposal is raising concerns, particularly from those who stand to see their pay reduced.

CMS officials estimate the proposal would save time. CMS Administrator Seema Verma said that the documentation change would result in an additional 51 hours for patient care per clinician per year.

Lisa Gangarosa, MD, AGAF, chair, AGA Government Affairs Committee, said that CMS should be commended for trying to reduce administrative burdens. "Unfortunately, in their efforts to reduce burden, CMS has proposed changes that drastically undervalue the care gastroenterologists and hepatologists provide to patients with inflammatory bowel disease, motility disorders, chronic liver disease, and other complex gastrointestinal diseases."

Angus B. Worthing, MD, chair of the American College of Rheumatology's Committee on Government Affairs, said he was doubtful that any increase in volume would offset the losses from the proposed flat payment across levels 2-5 E/M visits, especially if the pay decrease results in access issues.

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SOURCE: CMS proposed rule, CMS-1693-P.

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FROM THE AGA JOURNALS

Study examines POEM learning curve

BY AMY KARON
MDedge News

Technical failures or adverse events complicated 4% of peroral endoscopic myotomies (POEMs) in a large single-center retrospective study.

Individual predictors of this composite negative outcome included case number, full-thickness myotomy, and procedure time, Zuqiang Liu, PhD, and his associates at Fudan University, Shanghai, China, wrote in the September issue of Clinical Gastroenterology and Hepatology.

After these risk factors were controlled, the composite rate of adverse events and technical failures dropped gradually after an endoscopist had performed his or her first 100 cases, according to the researchers. "Technical proficiency, demonstrated by plateauing of the procedure time, could be achieved after 70 cases," they wrote. "The volume of cases required to manage challenging situations and prevent adverse events was thus higher than that needed for simple technical proficiency." The experience of the training surgeon helped trainees gain technical proficiency faster, they added.

POEM is minimally invasive and effectively treats spastic esophageal motility disorders. However, it is also a challenging procedure, and little is known about its learning curve. For the study, the researchers retrospectively reviewed technical failures and adverse events in 1,346 POEMs performed for achalasia at a single hospital in China between August 2010 and July 2015. They also assessed procedure time and a secondary composite outcome consisting of technical failure, adverse events, and clinical failure (further symptoms) for the first 192 cases performed by the original training surgeon.

There were 10 technical failures and 44 adverse events affecting a total of 54 patients (4%). Case number (P = .010), full-thickness myotomy (P = .002), and procedure time (P = .001) independently predicted this primary composite outcome. Adjusted cumulative sum analysis showed that the rate of this composite outcome decreased gradually after a surgeon had performed his or her first 100 cases. "The procedure time was high during the first few cases and decreased after endoscopists performed 70 cases," indicating technical proficiency, the investigators wrote. The rate of the secondary composite outcome also fell gradually after the primary surgeon had performed between 90 and 100 cases.

For the first 192 cases performed by the lead surgeon, postprocedural follow-up time was typically 59 months, with a range of 3-71 months. Clinical failures occurred in 20 cases (10%). Rates of clinical failure were 6% at 1 year, 8% at 2 years, and 10% at 3 years.

This is the first study and the largest POEM database so far to assess the learning curve for this procedure by evaluating adverse events and clinical and technical failure, said the researchers. Previous studies consisted of small cases, usually of less than 100 patients each, they added. Such studies would inherently be biased because the smaller the caseload, the longer it might take for the learning curves of surgeons to plateau, they added.

Funders included the National Natural Science Foundation of China, the Major Project of Shanghai Municipal Science and Technology Committee, the Chen Guang Program of Shanghai Municipal Education Commission, and the Outstanding Young Doctor Training Project of Shanghai Municipal Commission of Health and Family Planning. The investigators reported no relevant conflicts of interest.

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SOURCE: Liu Z et al. Clin Gastroenterol Hepatol. 2017 Dec 5. doi: 10.1016/j.cgh.2017.11.048.

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aries) but also a large portion of research and education costs. Loss of 340b pharmacy income, the more government payers, CMS regulations and potential penalties, and narrowing clinical networks all have reduced revenue for many AMCs. Adding these proposed rule changes will send many AMCs further into negative margins: This will affect training of our next-generation leaders and discoveries of new science.

John I. Allen, MD, MBA, AGAF, professor of medicine, division of gastroenterology, University of Michigan School of Medicine, Ann Arbor. He reported no conflicts.

Determining competency in endoscopic procedures has been a vexing challenge since the introduction of flexible endoscopy. Traditionally, procedure volume has been used as a surrogate for technical competence. However, each endoscopist has their own learning curve. Furthermore, that curve is influenced by both the endoscopist and the characteristics of each patient. Thus, relying on procedure volume or length of time are likely inadequate markers of the true learning process. It has become more important to rely on more sophisticated measurements of competence, as illustrated in this study by Liu et al.

DR. PATEL

By using a large database of patients undergoing POEM, the authors applied risk-adjusted cumulative sum and moving averages (CUSUM) analysis to develop individual learning curves of six training endoscopists. The primary outcomes used to develop the curve were technical failure and adverse effects (likely the two outcomes patients are most concerned about). The analysis was adjusted for case complexity as well, reflecting that not all training episodes are the same. The results reveal that, although trainee endoscopists were able to perform POEM "quickly" by 70 cases, they did not achieve the more important primary outcomes of technical success and low adverse events until at least 100 procedures. This is akin to the difference between getting to the cecum quickly and having a high adenoma detection rate in colonoscopy.

Moving forward, using sophisticated measurement of individual endoscopists' learning curves will allow maximal effectiveness of routine procedures such as colonoscopy.

Kal Patel, MD, is associate professor of medicine, Baylor College of Medicine, Houston. He has no conflicts of interest.

Pancreatic surveillance identified resectable cancers

BY AMY KARON
MDedge News

Long-term pancreatic surveillance of high-risk patients identified cancers while they were still resectable, and 85% of such patients remained alive 3 years after diagnosis, researchers reported.

"Among individuals undergoing pancreatic surveillance, specific detectable lesions with worrisome features predicted neoplastic progression. The short-term outcomes of patients with screening-detected PDACs [pancreatic ductal adenocarcinomas] improved," wrote Marcia Irene Canto, MD, MHS, of the Johns Hopkins University, Baltimore, together with her associates in the September issue of Gastroenterology.

The lifetime risk of PDAC is about 1.5%, the researchers noted. Consequently, the U.S. Preventive Services Task Force does not recommend pancreatic surveillance at a population level. However, pancreatic screening is being evaluated for individuals who are at elevated risk of PDAC, including those with at least two first-degree relatives with PDAC or who have germline mutations in BRCA1, BRCA2, PALB2, PRSS1 (hereditary pancreatitis), CDKN2A, MLH1, MSH2, MSH6, PMS2 (Lynch syndrome), or STK11 (Peutz-Jeghers syndrome).

For the study, Dr. Canto and her associates analyzed data from 354 such high-risk individuals

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FROM THE AGA JOURNALS

Nerve growth factor therapy speeds gastric ulcer healing

BY WILL PASS
MDedge News

Nerve growth factor (NGF) therapy in aging rats improves angiogenesis and speeds gastric ulcer healing, which suggests possible applications in human medicine, a recent study found.

Compared with young individuals, elderly people have significantly lower levels of NGF in gastric endothelial cells (GECs), a finding that is associated with impaired angiogenesis and delayed gastric ulcer healing.

"Our previous studies have shown that the gastric mucosa of aging individuals ... has increased susceptibility to injury and delayed healing owing to impaired angiogenesis, but the mechanisms are not fully elucidated," wrote Amrita Ahluwalia, PhD, of Medical and Research Services at the Veterans Affairs Long Beach (Calif.) Healthcare System and her coauthors.

Mapping the drivers of angiogenesis in the gastric mucosa could lead to treatment options for elderly patients with injured or ulcerated gastric tissue. In prior trials (with rats), "treatment with VEGF [vascular endothelial growth factor] only partly reversed impaired angiogenesis in aging [GECs], indicating an essential role for other factor(s) in addition to VEGF," the investigators wrote in Cellular and Molecular Gastroenterology and Hepatology. They looked to NGF as another possible factor because recent studies had shown it could improve angiogenesis in the brain.

The present study measured NGF expression in rats and humans of varying ages, with NGF treatment and gene therapy performed in rats (in vitro and in vivo).

In vitro angiogenesis was 4.1-fold lower in GECs from aging rats (24 months of age) than it was in GECs from young rats (3 months of age; *P* less than .001). NGF protein and NGF mRNA levels were also significantly lower in aging GECs than they were with young GECs (NGF protein, 3.0-fold lower; NGF mRNA, 4.2-fold lower; *P* less than .001).

Treatment of aging rat GECs with exogenous NGF increased angiogenesis by 1.5-fold (*P* less than .001). Pretreatment with a PI3 kinase inhibitor or an mTOR inhibitor abolished this improvement, suggesting that the PI3 kinase/Akt and mTOR pathways are involved.

When NGF gene therapy was performed in aging GECs, NGF levels rose to the level of that in young GECs, with restoration of angiogenesis (threefold increase; *P* less than .001). Proliferation of aging GECs also increased with gene therapy (*P* less than .001).

In vivo studies revealed that NGF expression and cell proliferation in aging rat gastric mucosa were lower than in younger rats. Older rats treated with local NGF protein showed increased gastric mucosa angiogenesis and faster ulcer healing, compared with phosphate-buffered saline treatment.

Similar age-related NGF declines were found in humans. When gastric mucosa biopsies were collected from younger individuals (younger than 40 years old; n = 10) and compared with samples from an older population (at least 70 years old; n = 10), the investigators found that NGF expression was 5.5-fold lower in the older people (*P* less than .001).

"This clearly indicates human relevance of our experimental findings and also can explain impaired angiogenesis and delayed healing of injured gastric mucosa in aging individuals," the investigators wrote.

"Aging gastropathy and its consequences are clinically critical issues," the investigators noted, "especially because the aging U.S. population is growing rapidly and it is estimated that, by the year 2030, approximately 70 million Americans will be older than 65 years of age." Gastric ulcers become more common with age, and individuals 70 years or older have an eightfold increased risk of associated complications, compared with people under 50 years.

The study was funded by the Department of Veterans Affairs Biomedical Laboratory Research and Development Service. The authors declared no conflicts of interest.

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SOURCE: Ahluwalia A et al. CMGH. 2018 May 17. doi: 10.1016/j.jcmgh.2018.05.003.

Although the incidence of gastric ulcers has been declining in the general population, hospitalization and mortality linked to gastric ulcers remains high in the elderly population. One of the major risk factors for gastric ulceration is the use of NSAIDs.


DR. ENGEVIK

This study described a new role for nerve growth factor (NGF) in promoting angiogenesis during gastric ulcer repair. The authors observed that aged rats exhibited low NGF levels in gastric endothelial cells that corresponded with impaired ulcer healing of the gastric mucosa following injury. Local NGF treatment to aged rats significantly increased angiogenesis and gastric regeneration. Consistent with their in vivo rat model, analysis of human gastric biopsy specimens showed that individuals more than 70 years of age had decreased expression of NGF in gastric endothelial cells, compared with individuals younger than 40 years.

Ahluwalia and colleagues are the first to demonstrate the role of NGF in aging gastropathy, and their work highlights a key mechanism of angiogenesis during gastric repair that may inform future therapeutic strategies.

Amy Christine Engevik, PhD, is a postdoctoral fellow in the division of surgical sciences at Vanderbilt University Medical Center, Nashville, Tenn. She has no conflicts of interest.

Continued from previous page

enrolled in the CAPS (Cancer of the Pancreas Screening) cohort studies, which were conducted at tertiary care academic centers during 1998-2014. All participants underwent endoscopic ultrasound at baseline, followed by surveillance with endoscopic ultrasound, magnetic resonance imaging, computed tomography, or some combination of these modalities. Patients who developed pancreatic cancer or high-grade dysplasia were offered surgery.

In all, 68 patients (19%) developed pancreatic lesions with worrisome features, such as solid masses, multiple cysts, mural nodules, thickened or enhancing walls, cysts exceeding 3 cm in size or that grew more than 4 mm annually, a greater than 5-mm dilation of the main pancreatic duct, or an abrupt change in duct caliber. The lesions developed over a median of 13.1 months (interquartile range, 0.2-52 months).

A total of 7% of patients had neoplastic progression, including 14 cases of PDAC and 10 cases of high-grade dysplasia. Median times from baseline to detection of PDAC were 4.8 years overall (IQR, 1.6-6.9 years), 1.7 years in patients aged at least 60 years at baseline (IQR, 0.5-4.4 years), and 5.2 years in younger patients (IQR, 0.4-8 years). Patients developed PDAC at a median of 67 years old.

Among 10 PDACs detected by surveillance, 9 were resectable. Three patients subsequently died of PDAC, while one patient died of complications of gastric cancer surgery. However, 85% of patients survived for at least 3 years after surgical resection of PDAC. The remaining four cases of PDAC were detected outside surveillance or after patients stopped surveillance.

The 10 cases of high-grade dysplasia consisted of intraductal papillary mucinous neoplasm with high-grade dysplasia or high-grade pancreatic intraepithelial neoplasia. Patients whose PDAC or high-grade dysplasia was detected by surveillance survived a median of 5.3 years, while patients whose surveillance was late or stopped and who later developed neoplasia survived a median of only 1.4 years after diagnosis (*P* less than .0001).

Funders included the Pancreatic Cancer Action Network, Lustgarten Foundation for Pancreatic Cancer Research, the John and Peter Hooven Memorial Endowment, Hugh and Rachel Victor, and ChiRhoClin. Dr. Canto had no disclosures. Three coinvestigators disclosed royalties for licensing of PALB2 as a pancreatic cancer susceptibility gene.

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SOURCE: Canto MI et al. Gastroenterology. 2018 May 24. doi: 10.1053/j.gastro.2018.05.035.

FROM THE AGA JOURNALS

Even modest alcohol use may worsen NAFLD

BY AMY KARON
MDedge News

PATIENTS with nonalcoholic fatty liver disease (NALFD) who consumed modest quantities of alcohol had significantly less improvement in steatosis and significantly lower odds of resolution of nonalcoholic steatohepatitis (NASH), compared with nondrinkers, according to the results of a longitudinal cohort study published in the September issue of Clinical Gastroenterology and Hepatology.

Modest drinkers also had significantly less improvement in their AST levels, compared with nondrinkers, said Veeral Ajmera, MD, of the University of California, San Diego, and his associates. "Importantly, our results suggest that cessation of alcohol use may mitigate these changes," they wrote. Clinicians should consider the spectrum of NAFLD, and especially NASH, when making recommendations about alcohol use. "More advanced NAFLD severity may warrant counseling against [even] modest alcohol use."

More than one in three adults in the United States has NAFLD and about two-thirds drink alcohol, almost always in moderation, the researchers noted. Modest alcohol use has been linked to decreased cardiovascular risk.

More than one in three adults in the United States has NAFLD and about two-thirds drink alcohol, almost always in moderation, the researchers noted. Modest alcohol use has been linked to decreased cardiovascular risk, which is particularly relevant because patients with NAFLD tend to have risk factors for cardiovascular disease. Results from at least two cross-sectional studies also suggest modest drinkers with NAFLD have less severe histology, includ-

Continued on following page

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FROM THE AGA JOURNALS

Avatrombopag cut transfusions in chronic liver disease

BY AMY KARON
MDedge News

Once-daily treatment with the oral second-generation thrombopoietin agonist avatrombopag (Doptelet) significantly reduced the need for platelet transfusion and rescue therapy for up to 7 days after patients with chronic liver disease and thrombocytopenia underwent scheduled procedures, according to the results of two international, randomized, double-blind, phase III, placebo-controlled trials reported in the September issue of Gastroenterology.

In the ADAPT-1 trial (231 patients), 66% of patients in the 60-mg arm met this primary endpoint, as did 88% of patients who received 40 mg, versus 23% and 38% of the placebo arms, respectively (*P* less than .001 for each comparison). In the ADAPT-2 trial (204 patients), 69% of the 60-mg group met the primary endpoint, as did 88% of the 40-mg group, versus 35% and 33% of the respective placebo groups (*P* less than .001 for each comparison).

These results led the Food and Drug Administration to approve avatrombopag in May 2018 under its priority review process. The novel therapy "may be a safe and effective alternative to platelet transfusions" that could simplify the clinical management of patients with chronic liver disease and thrombocytopenia, Norah Terrault, MD, MPH, and her associates wrote.

In each trial, patients were randomized on a 2:1 basis to receive oral avatrombopag or placebo once daily for 5 days. Patients in the intervention arms received 60 mg avatrombopag if their baseline platelet count was less than 40 x 10^9 per liter, and 40 mg if their baseline platelet count was 40-50 x 10^9 per liter. Procedures were scheduled for 10-13 days after treatment initiation.

"Platelet counts increased by [treatment] day 4, peaked at days 10-13, and then returned to baseline levels by day 35," the researchers reported. In ADAPT-1 patients with low baseline counts, 69% of avatrombopag recipients reached a prespecified target of at least 50 x 10^9 platelets per liter on their procedure day, versus 4% of placebo recipients (*P* less than .0001). Corresponding proportions in ADAPT-2 were 67% and 7%, respectively (*P* less than .0001). Among patients with higher baseline counts, 88% and 20% achieved the target, respectively, in ADAPT-1 (*P* less than .0001), as did 93% versus 39%, respectively, in ADAPT-2 (*P* less than .0001).

Avatrombopag and placebo produced similar rates of treatment-emergent adverse events. Only three avatrombopag patients developed platelet counts above 200 x 10^9 per liter, and they all remained asymptomatic, the investigators said.

Dova Pharmaceuticals makes avatrombopag and provded medical writing support. Dr. Terrault and three coinvestigators disclosed ties to AbbVie, Allergan, Bristol-Myers Squibb, and other such companies. One coinvestigator is chief medical officer of Dova, helped analyze the data, write the manuscript, and gave final approval of the submitted version.

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SOURCE: Terrault N et al. Gastroenterology. 2018 May 17. doi: 10.1053/j.gastro.2018.05.025.

Thrombocytopenia in cirrhosis is frequent and multifactorial. Severe thrombocytopenia (less than 50/nL) is rare in cirrhotic patients, but when it occurs may prevent required procedures from being performed or require platelet transfusions, which are associated with significant risks.


DR. TILLMANN

Previous attempts to increase platelets in cirrhotic patients with thrombopoietin agonists were halted because of increased frequency of portal vein thrombosis and hepatic decompensation.

Now avatrombopag has been licensed with a 5-day regimen to increase platelets prior to elective interventions in severely thrombocytopenic (less than 50/nL) patients with chronic liver disease with a seemingly better safety profile than earlier treatments and good efficacy. The patient groups studied in the licensing trial had slightly milder but not significantly different liver disease, compared with those in the eltrombopag studies. The key difference was a pretreatment requirement of a portal vein flow of more than 10 cm/sec prior to enrollment, which likely reduced the risk of portal vein thrombosis. It is important that providers ready to use avatrombopag are aware of this.

No data are currently available for patients with a Model for End-Stage Liver Disease score greater than 24, and very limited data are available for patients with Child B and Child C cirrhosis. Given this limitation, careful judgment will be needed; a pretreatment portal vein flow may be advisable, though not a label requirement. An observational study, NCT03554759 is ongoing and will further confirm the likely safety of avatrombopag.

Hans L. Tillmann, MD, is a clinical associate professor, East Carolina University, Greenville, and staff physician, Greenville (N.C.) VA Health Care Center. He has no conflicts of interest.

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Continued from previous page

ing less NASH and fibrosis. However, modest drinkers tend to be more physically active, with lower body mass indexes, higher physical activity levels, and less obesity, which are potential confounders. To better understand the effects of modest alcohol consumption on NAFLD, the researchers studied adults with NAFLD who participated in studies conducted by the multicenter NASH Clinical Research Network.

The 285 participants were typically aged in their late 40s, female, white, and obese, with an average body mass index of 34.7 kg/m^2. In all, 168 participants (59%) reported consuming up to two drinks per day, while 41% abstained from alcohol use. During an average of 47 months between biopsies (standard deviation, 26 months), nondrinkers averaged a 0.49 reduction in steatosis grade, significantly more than that of modest drinkers (reduction, 0.30; *P* = .04). Nondrinkers also had a greater decrease in mean AST level (7 U/L), compared with drinkers (2 U/L; *P* = .04).

A total of 64% of patients were classified as having definite NASH, 19% had NAFLD without NASH, and 17% had borderline NASH. At baseline, 23% of patients did not have fibrosis, 32% had stage 1 fibrosis, 21% had stage 2, 21% had stage 3, and 3% had stage 4. Modest drinkers were more likely to be white and were less likely to be diagnosed with definitive NASH at baseline. After these potential confounders were controlled, modest drinkers had significantly lower odds of NASH resolution, compared with nondrinkers (adjusted odds ratio, 0.32; 95% confidence interval, 0.11-0.92; *P* = .04).

"[The] presence of NASH has consistently been shown to predict increased risk for fibrosis progression, and therefore, our finding of less NASH resolution among consistent modest drinkers is clinically relevant," the investigators wrote. "Although we were unable to assess the association between modest alcohol consumption and cardiovascular risk, we did not see any significant changes in measured metabolic risk factors with known associations with cardiovascular disease including low-density lipoprotein and high-density lipoprotein cholesterol and insulin resistance."

Funders of the study included the National Institute of Diabetes and Digestive and Kidney Diseases, the National Center for Advancing Translational Sciences, the Advanced/Transplant Hepatology Fellowship, the American Association for the Study of Liver Diseases Foundation, and the Intramural Research Program of the National Institutes of Health.

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SOURCE: Ajmera V et al. Clin Gastroenterol Hepatol. 2018 Mar 14. doi: 10.1016/j.cgh.2018.01.026.

FOR TREATING CHRONIC HCV **EXPAND WHAT'S POSSIBLE**

INDICATION

EPCLUSA (sofosbuvir 400 mg/velpatasvir 100 mg tablets) is indicated for the treatment of adults with chronic hepatitis C virus (HCV) **genotype (GT) 1, 2, 3, 4, 5, or 6** infection without cirrhosis or with compensated cirrhosis and in combination with ribavirin for those with decompensated cirrhosis.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN HCV/HBV COINFECTED PATIENTS

Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with EPCLUSA. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct acting antivirals (DAAs) and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Cases have been reported in patients who are HBsAg positive, in patients with serologic evidence of resolved HBV, and also in patients receiving certain immunosuppressant or chemotherapeutic agents; the risk of HBV reactivation associated with treatment with HCV DAAs may be increased in patients taking these other agents. Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

Contraindications

- If EPCLUSA is used in combination with ribavirin (RBV), all contraindications, warnings and precautions, in particular pregnancy avoidance, and adverse reactions to RBV also apply. Refer to RBV prescribing information.

Warnings and Precautions

- **Serious Symptomatic Bradycardia When Coadministered with Amiodarone:** Amiodarone is not recommended for use with EPCLUSA due to the risk of symptomatic bradycardia, particularly in patients also taking beta blockers or with underlying cardiac comorbidities and/or with advanced liver disease. A fatal cardiac arrest was reported in a patient taking amiodarone who was coadministered a sofosbuvir containing regimen. In patients without alternative, viable treatment options, cardiac monitoring is recommended. Patients should seek immediate medical evaluation if they develop signs or symptoms of bradycardia.
- **Risk of Reduced Therapeutic Effect Due to Concomitant Use of EPCLUSA with P-gp Inducers and/or Moderate to Potent Inducers of CYP2B6, CYP2C8 or CYP3A4:** Rifampin, St. John's wort, and carbamazepine are not recommended for use with EPCLUSA as they may significantly decrease sofosbuvir and/or velpatasvir plasma concentrations.

WHAT DOES SIMPLE DOSING LOOK LIKE?

1

TABLET ONCE A DAY

TAKEN WITH OR WITHOUT FOOD

The dosing information above does not include patients with decompensated cirrhosis (Child-Pugh B or C).

EPCLUSA HAS THE SAME 12-WEEK DOSING REGIMEN FOR MOST HCV PATIENTS REGARDLESS OF TREATMENT HISTORY, GENOTYPE (1-6), OR THE PRESENCE OF COMPENSATED CIRRHOSIS[1]

- Test all patients for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating HCV treatment with EPCLUSA[1]

IMPORTANT SAFETY INFORMATION

Adverse Reactions

- The most common adverse reactions (≥10%, all grades) with EPCLUSA were headache and fatigue; and when used with RBV in decompensated cirrhotics were fatigue, anemia, nausea, headache, insomnia, and diarrhea.

Drug Interactions

- Coadministration of EPCLUSA is not recommended with topotecan due to increased concentrations of topotecan.
- Coadministration of EPCLUSA is not recommended with proton-pump inhibitors, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifapentine, efavirenz, and tipranavir/ritonavir due to decreased concentrations of sofosbuvir and/or velpatasvir.

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

Please see Brief Summary of full Prescribing Information for EPCLUSA, including **BOXED WARNING**, on the following pages.

Compensated cirrhosis = Child-Pugh A, RBV = ribavirin, TE = treatment-experienced (subjects who have failed a peginterferon alfa + RBV–based regimen with or without an HCV protease inhibitor [boceprevir, simeprevir, or telaprevir]), TN = treatment-naïve

An increasing number of insurance plans cover EPCLUSA for GT 1 patients[2]

EPCLUSA®
sofosbuvir/velpatasvir
400 mg/100 mg tablets

LEARN MORE AT HCP.EPCLUSA.COM

EPCLUSA® (sofosbuvir 400 mg and velpatasvir 100 mg) tablets, for oral use

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

BOXED WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV

Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with EPCLUSA. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct acting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and post treatment follow up. Initiate appropriate patient management for HBV infection as clinically indicated.

INDICATIONS AND USAGE

EPCLUSA is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection:

- Without cirrhosis or with compensated cirrhosis
- With decompensated cirrhosis for use in combination with ribavirin

CONTRAINDICATIONS

EPCLUSA and ribavirin (RBV) combination regimen is contraindicated in patients for whom ribavirin is contraindicated. Refer to the RBV prescribing information for a list of contraindications for RBV.

WARNINGS AND PRECAUTIONS

Risk of HBV Reactivation in Patients Coinfected with HCV and HBV: HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct acting antivirals and who were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients with serologic evidence of resolved HBV infection (HBsAg negative and hepatitis B core antibody (anti-HBc) positive). HBV reactivation has also been reported in patients receiving certain immunosuppressant or chemotherapeutic agents; the risk of HBV reactivation associated with treatment with HCV direct-acting antivirals may be increased in these patients. HBV reactivation is characterized as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level. In patients with resolved HBV infection, reappearance of HBsAg can occur. Reactivation of HBV replication may be accompanied by hepatitis, i.e., increase in aminotransferase levels; and, in severe cases, increases in bilirubin levels, liver failure, and death can occur. Test all patients for evidence of current or prior HBV infection by measuring HBsAg and anti-HBc before initiating HCV treatment with EPCLUSA. In patients with serologic evidence of HBV infection, monitor for clinical and laboratory signs of hepatitis flare or HBV reactivation during HCV treatment with EPCLUSA and during posttreatment follow up. Initiate appropriate patient management for HBV infection as clinically indicated.

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

Risk of Reduced Therapeutic Effect Due to Concomitant Use of EPCLUSA With Inducers of P-gp and/or Moderate to Potent Inducers of CYP: Drugs that are inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., rifampin, St. John's wort, carbamazepine) may significantly decrease plasma concentrations of sofosbuvir and/or velpatasvir, leading to potentially reduced therapeutic effect of EPCLUSA.

Risks Associated with RBV and EPCLUSA Combination Treatment: If EPCLUSA is administered with RBV, the warnings and precautions for RBV apply to this combination regimen. Refer to the RBV prescribing information for a full list of the warnings and precautions for RBV.

ADVERSE REACTIONS

Most common adverse reactions (greater than or equal to 10%, all grades) with EPCLUSA for 12 weeks were headache and fatigue; EPCLUSA and ribavirin for 12 weeks in patients with decompensated cirrhosis were fatigue, anemia, nausea, headache, insomnia, and diarrhea.

Subjects without Cirrhosis or with Compensated Cirrhosis: The adverse reactions data for EPCLUSA in patients without cirrhosis or with compensated cirrhosis were derived from three Phase 3 clinical trials (ASTRAL-1, ASTRAL-2, and ASTRAL-3) which evaluated a total of 1035 subjects infected with genotype 1, 2, 3, 4, 5, or 6 HCV, who received EPCLUSA for 12 weeks. The proportion of subjects who permanently discontinued treatment due to adverse events was 0.2% for subjects who received EPCLUSA for 12 weeks. The most common adverse reactions (at least 10%) were headache and fatigue in subjects treated with EPCLUSA for 12 weeks. Adverse reactions (all grades) reported in ≥5% of subjects receiving 12 weeks of treatment with EPCLUSA in ASTRAL-1 were: headache (22%), fatigue (15%), nausea (9%), asthenia (5%), and insomnia (5%). Of subjects receiving EPCLUSA who experienced these adverse reactions, 79% had an adverse reaction of mild severity (Grade 1). The adverse reactions observed in subjects treated with EPCLUSA in ASTRAL-2 and ASTRAL-3 were consistent with those observed in ASTRAL-1. Irritability was also observed in greater than or equal to 5% of subjects treated with EPCLUSA in ASTRAL-3.

Subjects Coinfected with HCV and HIV-1: The safety assessment of EPCLUSA in subjects with HCV/HIV-1 coinfection was based on an open-label trial (ASTRAL-5) in 106 subjects who were on stable antiretroviral therapy. The safety profile in HCV/HIV-1 coinfected subjects was similar to HCV mono-infected subjects. The most common adverse reactions (at least 10%) were fatigue (22%) and headache (10%).

Subjects with Decompensated Cirrhosis: The safety assessment of EPCLUSA in subjects infected with genotype 1, 2, 3, 4, or 6 HCV with decompensated cirrhosis was based on one Phase 3 trial (ASTRAL-4) including 87 subjects who received EPCLUSA with ribavirin for 12 weeks. On the first day of treatment with EPCLUSA with ribavirin, 6 subjects and 4 subjects were assessed to have Child-Pugh A and Child-Pugh C cirrhosis, respectively. The most common adverse reactions (all grades with frequency of 10% or greater) in the 87 subjects who received EPCLUSA with ribavirin for 12 weeks were fatigue (32%), anemia (26%), nausea (15%), headache (11%), insomnia (11%), and diarrhea (10%). Of subjects who experienced these adverse reactions, 98% had adverse reactions of mild to moderate severity. A total of 4 (5%) subjects permanently discontinued EPCLUSA with ribavirin due to an adverse event; there was no adverse event leading to discontinuation that occurred in more than 1 subject. Decreases in hemoglobin to less than 10 g/dL and 8.5 g/dL during treatment were observed in 23% and 7% subjects treated with EPCLUSA with ribavirin for 12 weeks, respectively. Ribavirin was permanently discontinued in 17% of subjects treated with EPCLUSA with ribavirin for 12 weeks due to adverse reactions.

Less Common Adverse Reactions Reported in Clinical Trials: *Rash*: In ASTRAL-1, rash occurred in 2% of subjects without cirrhosis or with compensated cirrhosis treated with EPCLUSA for 12 weeks and in 1% of subjects treated with placebo. In ASTRAL-4, rash occurred in 5% of subjects with decompensated cirrhosis treated with EPCLUSA with RBV for 12 weeks. No serious adverse reactions of rash occurred in either studies and all rashes were mild or moderate in severity. *Depression*: In ASTRAL-1, depressed mood occurred in 1% of subjects without cirrhosis or with compensated cirrhosis treated with EPCLUSA for 12 weeks and was not reported by any subject taking placebo. No serious adverse reactions of depressed mood occurred and all events were mild or moderate in severity.

Laboratory Abnormalities: *Lipase Elevations:* In ASTRAL-1, isolated, asymptomatic lipase elevations of greater than 3xULN were observed in 3% and 1% of subjects treated with EPCLUSA and placebo for 12 weeks, respectively and in 6% and 3% of subjects treated with EPCLUSA in ASTRAL-2 and ASTRAL-3, respectively. In the Phase 3 trial of subjects with decompensated cirrhosis (ASTRAL-4), lipase was assessed when amylase values were ≥1.5xULN. Isolated, asymptomatic lipase elevations of greater than 3xULN were observed in 2% of subjects treated with EPCLUSA with ribavirin for 12 weeks. *Creatine Kinase:*

Brief Summary (cont.)

In ASTRAL-1, isolated, asymptomatic creatine kinase elevations of greater than or equal to 10xULN was observed in 1% and 0% of subjects treated with EPCLUSA and placebo for 12 weeks, respectively; and in 2% and 1% of subjects treated with EPCLUSA in ASTRAL-2 and ASTRAL-3, respectively. In the Phase 3 trial with decompensated cirrhosis (ASTRAL-4), isolated, asymptomatic creatine kinase elevations greater than or equal to 10xULN were reported in 1% of subjects treated with EPCLUSA with ribavirin for 12 weeks. *Indirect Bilirubin:* Increases in indirect bilirubin up to 3 mg/dL above baseline were noted among HIV-1/HCV coinfected subjects treated with EPCLUSA and an atazanavir/ritonavir-based antiretroviral regimen. The elevated indirect bilirubin values were not associated with clinical adverse events and all subjects completed 12 weeks of EPCLUSA without dose adjustment or treatment interruption of either EPCLUSA or HIV antiretroviral agents.

Postmarketing Experience: 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. *Cardiac Disorders:* Serious symptomatic bradycardia has been reported in patients taking amiodarone who initiated treatment with sofosbuvir in combination with another HCV direct-acting antiviral. *Skin and Subcutaneous Tissue Disorders:* Skin rashes, sometimes with blisters or angioedema-like swelling; angioedema.

DRUG INTERACTIONS

Sofosbuvir and velpatasvir are substrates of P-gp and breast cancer resistance protein (BCRP) while GS-331007 (the predominant circulating metabolite of sofosbuvir) is not. Drugs that are inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., rifampin, St. John's wort, carbamazepine) may decrease plasma concentrations of sofosbuvir and/or velpatasvir, leading to reduced therapeutic effect of EPCLUSA. The use of these agents with EPCLUSA is not recommended. EPCLUSA may be coadministered with P-gp, BCRP, and CYP inhibitors. Velpatasvir is an inhibitor of drug transporters P-gp, BCRP, OATP1B1, OATP1B3, and OATP2B1. Coadministration of EPCLUSA with drugs that are substrates of these transporters may increase the exposure of such drugs. Fluctuations in international normalized ratio (INR) may occur in patients on concomitant warfarin; frequent monitoring of INR is recommended during EPCLUSA treatment and post-treatment follow-up.

Established and Potentially Significant Drug Interactions: The drug interactions are based on studies conducted with either EPCLUSA, the components of EPCLUSA (sofosbuvir and velpatasvir) as individual agents, or are predicted drug interactions that may occur with EPCLUSA. This list includes potentially significant interactions but is not all inclusive.

Alteration in Dose or Regimen May Be Recommended For The Following Drugs When Coadministered With EPCLUSA:

- **Acid Reducing Agents:** Velpatasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of velpatasvir. *Antacids:* Separate antacid and EPCLUSA administration by 4 hours. *H_2-receptor antagonists:* Doses comparable to famotidine 40 mg twice daily or lower may be administered simultaneously with or 12 hours apart from EPCLUSA. *Proton-pump inhibitors:* Coadministration of omeprazole or other proton pump inhibitors is not recommended. If considered medically necessary to coadminister, EPCLUSA should be administered with food and taken 4 hours before omeprazole 20 mg. Use with other proton pump inhibitors has not been studied.
- **Antiarrhythmics (amiodarone; digoxin):** *Amiodarone*: Coadministration of amiodarone with a sofosbuvir-containing regimen may result in serious symptomatic bradycardia and is not recommended. Mechanism of effect is unknown. If coadministration is required, cardiac monitoring is recommended. *Digoxin*: Increased concentration of digoxin. Monitor digoxin therapeutic concentration during coadministration with EPCLUSA. Refer to digoxin prescribing information for monitoring and dose modification recommendations for concentrations increases of less than 50%.
- **Anticancers (topotecan):** Increased concentration of topotecan. Coadministration is not recommended
- **Anticonvulsants (carbamazepine; phenytoin; phenobarbital; oxcarbazepine):** Decreased sofosbuvir and velpatasvir concentrations leading to reduced EPCLUSA effect. Coadministration is not recommended.
- **Antimycobacterials (rifabutin; rifampin; rifapentine):** Decreased sofosbuvir and velpatasvir concentrations leading to reduced EPCLUSA effect. Coadministration is not recommended.
- **HIV Antiretrovirals (efavirenz; regimens containing tenofovir DF; tipranavir/ritonavir):**
  - *Efavirenz*: Decreased concentration of velpatasvir. Coadministration of EPCLUSA with efavirenz-containing regimens is not recommended.
  - *Regimens containing tenofovir disoproxil fumarate (DF)*: Due to increased tenofovir concentrations, monitor for tenofovir-associated adverse reactions. Refer to the prescribing information of the tenofovir DF-containing product for renal monitoring recommendations.
  - *Tipranavir/ritonavir*: Decreased sofosbuvir and velpatasvir concentrations leading to reduced EPCLUSA effect. Coadministration is not recommended.
- **Herbal Supplements (St. John's wort):** Decreased sofosbuvir and velpatasvir concentrations. Coadministration is not recommended.
- **HMG-CoA Reductase Inhibitors (rosuvastatin; atorvastatin):** *Rosuvastatin:* Significant increase in rosuvastatin concentrations and risk of rosuvastatin associated myopathy, including rhabdomyolysis. Rosuvastatin may be administered with EPCLUSA at a dose that does not exceed 10 mg. *Atorvastatin*: May be associated with increased risk of myopathy, including rhabdomyolysis. Monitor closely for HMG-CoA reductase inhibitor-associated adverse reactions, such as myopathy and rhabdomyolysis.

Drugs without Clinically Significant Interactions with EPCLUSA: Based on drug interaction studies conducted with the components of EPCLUSA (sofosbuvir or velpatasvir) or EPCLUSA, no clinically significant drug interactions have been observed with the following drugs. *EPCLUSA*: atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, dolutegravir, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, emtricitabine, raltegravir, or rilpivirine; *Sofosbuvir*: ethinyl estradiol/norgestimate, methadone, or tacrolimus; *Velpatasvir*: ethinyl estradiol/norgestimate, ketoconazole, or pravastatin.

USE IN SPECIFIC POPULATIONS

Pregnancy: If EPCLUSA is administered with RBV, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the RBV prescribing information. No adequate human data are available to establish whether or not EPCLUSA poses a risk to pregnancy outcomes.

Lactation: It is not known whether the components of EPCLUSA and its metabolites are present in human breast milk, affect human milk production, or have effects on the breastfed child. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for EPCLUSA and any potential adverse effects on the breastfed child from EPCLUSA or from the underlying maternal condition. If EPCLUSA is administered with RBV, the nursing mother's information for RBV also applies to this combination regimen. Refer to the RBV prescribing information.

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

Geriatric Use: Clinical trials of EPCLUSA included 156 subjects aged 65 and over (12% of total number of subjects in the Phase 3 clinical studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment of EPCLUSA is warranted in geriatric patients.

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

Hepatic Impairment: No dosage adjustment of EPCLUSA is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C).

References: 1. EPCLUSA US full Prescribing Information. Gilead Sciences, Inc. Foster City, CA. November 2017. **2.** Data on file. Gilead Hepatitis C Coverage Report from 11/15/17-03/26/18.

Registration now open for the Crohn's & Colitis Congress

Registration for the Crohn's & Colitis Congress,® the premier conference on inflammatory bowel disease (IBD), is open. The Crohn's & Colitis Congress, a partnership of the Crohn's & Colitis Foundation and the American Gastroenterological Association, will take place Feb. 7-9, 2019, at the Bellagio, in Las Vegas.

Led by committee chair Brent Polk, MD, AGAF, and co-chairs Maria T. Abreu, MD, AGAF, and David T. Rubin, MD, AGAF, invited faculty include IBD thought-leaders in the fields of GI, research investigation, surgery, pediatrics, advanced practice, IBD nursing, diet and nutrition, mental health, radiology, and pathology.

The 2019 Congress' agenda includes main sessions that will emphasize case studies and panel discussions. There will also be parallel sessions on basic and translational science for senior and junior investigators.

In addition, several pre-Congress workshops, taking place Feb. 7, will be available for selection.

There will also be plenty of social events and plenty of time to enjoy Las Vegas; including a Friday night Welcome Reception that should not be missed. It's a great opportunity to network and celebrate.

Abstract submissions for basic, translational, and clinical research will be accepted through Oct. 24.

To learn more and register, visit www.crohnscolitiscongress.org.

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The impact of researchers

If not for committed researchers, the biologics, anti–tumor necrosis factor treatments, and direct-acting antivirals that we rely on to treat patients would not exist.

The AGA Research Foundation provides funding to the talented investigators working to identify new treatments and diagnostics for patients with gastroenterological conditions. By investing in research today, we're ensuring better patient care tomorrow.

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AGA funds noteworthy microbiome research

Congrats to AGA Research Foundation grantee Amir Zarrinpar, MD, PhD, from UC San Diego whose new microbiome research has been published in Nature Communications. Dr. Zarrinpar — a former AGA Microbiome Junior Investigator Research Award recipient — used his AGA funding to study cyclical fluctuations in the gut microbiome and its effects on host metabolism. This new study in Nature Communications is an unexpected finding resulting from Dr. Zarrinpar's AGA research project with his collaborator Satchin Panda, PhD, and their colleagues in the Salk Institute.

The study, Antibiotic-induced microbiome depletion alters metabolic homeostasis by affecting gut signaling and colonic metabolism, finds that mice that have their microbiomes depleted with antibiotics have decreased levels of glucose in their blood and better insulin sensitivity. The research has implications for understanding the role of the microbiome in diabetes. It also could lead to better insight into the side effects seen in people who are being treated with high levels of antibiotics.

The next steps for Dr. Zarrinpar and his team are to better understand what bacterial metabolites can affect insulin sensitivity and to functionally manipulate the microbiome to alter gut signaling to treat diabetes and other metabolic diseases. We look forward to seeing additional research on this topic that can eventually translate into improvements in patient care.

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Strides in digestive cancer research: Two research projects

The AGA Research Foundation Research Awards Program includes two grants dedicated to digestive cancer research: the AGA–Caroline Craig Augustyn & Damian Augustyn Award in Digestive Cancer and the AGA–R. Robert & Sally Funderburg Research Award in Gastric Cancer.

Continue reading to learn about the novel research projects being conducted by our 2018 digestive cancer grant recipients.

AGA–Caroline Craig Augustyn & Damian Augustyn Award in Digestive Cancer
Ravikanth Maddipati, MD
University of Pennsylvania Hospital System, Philadelphia

Dr. Maddipati's research focuses on understanding and treating metastatic disease in pancreatic cancer. With this grant, Dr. Maddipati will use advanced lineage-traced mouse models and innovative bioengineering approaches to identify the molecular pathways involved in tumor cell cooperation and define the role of circulating tumor cell-clusters in pancreatic cancer progression. This work will lead to a noninvasive method for monitoring disease progression and response to treatment in pancreatic cancer patients.

AGA's take: Pancreatic cancer, namely pancreatic ductal adenocarcinoma, is one of the deadliest cancers in the U.S. The AGA Research Foundation is pleased to fund Dr. Maddipati's research. As a physician-scientist, he is in a unique position to translate findings from basic research, using preclinical models, to develop improved approaches to treating patients with pancreatic cancer.

AGA–R. Robert & Sally Funderburg Research Award in Gastric Cancer
Jingwu Xie, PhD
Indiana University, Indianapolis

Dr. Xie's research focuses on drug resistance in gastric cancer. His team recently had a monumental discovery — activated hedgehog signaling, via GLI1 and GLI2 gene up-regulation, is responsible for drug resistance in gastric cancer. Dr. Xie's AGA-funded research will work to identify novel ways to sensitize gastric cancer cells to drug treatment by suppressing GLI1 and GLI2 activity.

AGA's take: Gastric cancer is a very underfunded area of research in the U.S., and with limited treatment options for patients, there is a great need for novel research projects. The AGA Research Foundation is proud to fund Dr. Xie's research, which we believe has the potential to translate into a new treatment that will improve outcomes for gastric cancer patients.

To see the full class of 2018 AGA Research Foundation awardees, visit the Meet Our Awardees section of our website, www.gastro.org/foundation-awardees.

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DDSEP eight
Digestive Diseases Self-Education Program

Quick quiz

Q1. A 28-year-old woman with a history of Crohn's disease is 29 weeks pregnant. She has had an ileocolonic resection and continues to have a small enterocutaneous fistula. She is otherwise doing well, and is maintained on infliximab therapy. She is asking about the mode of delivery of her baby. She wants to know if she should have an elective cesarean delivery.

In which of the following clinical scenarios would a cesarean delivery be recommended?
A. Ileal pouch-anal anastomosis
B. Enterocutaneous fistula
C. Infliximab therapy
D. Active perineal Crohn's disease
E. Pyoderma gangrenosum

Q2. A 63-year-old man presents to your clinic for follow-up of his known cirrhosis. He had an upper endoscopy 1 month ago, where he was found to have large varices with no high-risk stigmata. The patient was placed on nadolol 20 mg daily, and is tolerating it without side effects. On physical exam, he has no clinical ascites. His vitals are as follows: temperature, 98.4° F; blood pressure, 114/75 mm Hg; heart rate 55 beats/minute.

What is the next most appropriate step to manage these varices?
A. Increase nadolol to 40 mg daily
B. Repeat EGD and perform variceal band ligation
C. Change nadolol to carvedilol
D. Continue current medical management

The answers are on pages 17-18.

DDSEP eight
Digestive Diseases Self-Education Program

Quick quiz answers

Q1. Correct answer: D

Rationale
There is a risk of perineal trauma with vaginal delivery, and therefore, patients with active perianal Crohn's disease should undergo cesarean delivery to avoid exacerbation of disease. Patients without a history of perianal disease or those with inactive perianal disease have a low rate of relapse, and cesarean delivery is not warranted. Aside from patients with active perineal disease, the mode of delivery should be left to the discretion of the obstetrician. None of the other choices above, including ileal pouch-anal

Continued on following page

Top patient cases

Physicians with difficult patient scenarios regularly bring their questions to the AGA Community to seek advice from colleagues about therapy and disease management options, best practices, and diagnoses.

In case you missed it, here are the most popular clinical cases shared in the forum recently:

1. Ulcerative colitis
A 24-year-old male with severe pancolitis is in remission and currently functioning well, but the attending GI is fearful that a relapse is impending based on a fecal calprotectin of 1258 in a "clinically stable patient on long-term maximal therapy."

2. Esophageal varices on warfarin
A 64-year-old patient with Child-Turcotte-Pugh (CTP) class A cirrhosis had an upper endoscopy that showed large esophageal varices with no prior history of bleeding. View Miguel Malespin, MD, take on this popular case in the August issue of AGA Perspectives.

3. Does he have IBS or what?
A 37-year-old male with psoriatic arthritis and abdominal pain experiences rectal bleeding and abnormal findings during colonoscopy.

4. Chronic pancolitis
Quite a few GI experts commented on next steps for this 77-year-old pancolitis patient who has refused biologics based on cost.

5. Pouchitis
This 40-year-old patient developed diarrhea, fever, abdominal pain, and other symptoms, with observed ulceration and inflammation in the pouch and proximally.

More clinical cases and discussions are at https://community.gastro.org/discussions.

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Continued from previous page

anastomosis, justify the decision to perform cesarean section.

Q2. Correct answer: D

Rationale
This patient is on nadolol, a nonselective beta-blocker, for the primary prophylaxis of large esophageal varices. The dose of nonselective beta-blockers should be increased in a stepwise manner until the maximum tolerated dose or until a resting heart rate of 50-55/min is met. Since this patient is already at target heart rate, there is no indication to increase the dose. Repeat endoscopy is not indicated to assess change in size of varices once initiated on nonselective beta-blockers and at target heart rate. The choice between beta-blockers or endoscopic variceal ligation depends on local resources and expertise, patient preference and characteristics, side effects, and contraindications. Carvedilol, a nonselective beta-blocker with vasodilatory properties, is a promising alternative therapy that deserves further evaluation. However, given that nadolol has achieved target heart rate and patient is tolerating it, there is no indication to change management.

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These are predominantly male diseases

Liver disease *from page 1*

will inform how best to allocate resources."

The study extracted its data from the Vital Statistic Cooperative and the Centers for Disease Control and Prevention. The investigators not only examined raw mortality numbers, but analyzed them for demographic and geographic trends, in analyses that controlled for age.

Cirrhosis

During the study period, 460,760 patients died from cirrhosis (20,661 in 1999 and 34,174 in 2016, an increase of 65.4%).

Men were twice as likely to die from cirrhosis. Young people aged 25-34 years had the highest rate of increase (3.7% over the entire period and 10.5% from 2009 to 2016). This was directly driven by parallel increases in both alcohol use disorder and alcohol-related liver diseases, which increased by about 16% and 10%, respectively, in this group.

Native Americans had the highest mortality rate (25.8 per 100,000) followed by whites (12.7 per 100,000). "Notably, by 2016, cirrhosis accounted for 6.3% [up from 4.3% in 2009] and 7% [up from 5.8% in 2009] of deaths for Native Americans aged 25-34 and 35 or more, respectively," and 2.3% of all deaths among adults aged 25-34 years, the authors wrote.

The increases were largely felt in the southern and western states (about 13 per 100,000 in each region). The greatest increases occurred in Kentucky (6.8%), New Mexico (6%), Arkansas (5.7%), Indiana (5%), and Alabama (5%). There was a statistically significant 1.2% decrease in deaths from cirrhosis in Maryland.

Hepatocellular carcinoma

Hepatocellular carcinoma accounted for 136,442 deaths during the study period (5,112 in 1999 and 11,073 in 2016 – an increase of 116.6%). This represented an average annual increase of 2%.

Men were four times more likely to die from hepatocellular carcinoma. The increase manifested mostly in older people, decreasing in those younger than 55 years. Mortality was highest among Asians and Pacific Islanders (6 per 100,000), followed by blacks (4.94 per 100,000).

The increases were largely felt in western states, with an overall increase of 4.2 per 100,000.

"Many of the same states with worsening cirrhosis-related mortality also experienced worsening mortality from hepatocellular carcinoma, including Oregon and Iowa," the authors wrote. But mortality from the disease also increased significantly in Arizona (5.1%), Kansas (4.3%), Kentucky (4%), and Washington (3.9%).

"Potential explanations supported by these data include increasing early detection of hepatocellular carcinoma, application of curative or locoregional therapies, and, because hepatitis B is the principal cause of hepatocellular carcinoma worldwide and among Asian Americans, effectiveness of vaccination programs and the efficacy of antiviral therapy for hepatitis B in preventing the development of hepatocellular carcinoma."

However, they noted, "it is unclear how these trends are, or will be, affected by direct-acting antivirals for hepatitis C virus. ... Eradication of hepatitis C virus will prevent the development of cirrhosis and its complications, potentially changing these trends in the next 5-10 years. However, therapy for hepatitis C viral infection cannot modify the statistically significant trends observed related to alcohol or the expected increase in the burden of nonalcoholic fatty liver disease."

Neither author had any financial disclosure relevant to the work.

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SOURCE: Tapper EB et al. BMJ. 2018;362:k2817.

Weight gain linked to progression of fibrosis in NAFLD

BY JEFF CRAVEN
MDedge News

Study participants with nonalcoholic fatty liver disease (NAFLD) who were obese or gained weight were at an increased risk of fibrosis progression, while participants who lost weight had a reduced risk, according to recent research published in Clinical Gastroenterology and Hepatology.

Researchers evaluated 40,700 Korean adults (minimum age, 18 years) with NAFLD who underwent health screenings during 2002-2016 with a median 6-year follow-up. Patients were categorized and placed into weight quintiles based on whether they lost weight (quintile 1, 2.3-kg or greater weight loss; quintile 2, 2.2-kg to 0.6-kg weight loss), gained weight (quintile 4, 0.7- to 2.1-kg weight gain; quintile 5, at least 2.2-kg or greater weight gain) or whether their weight remained stable (quintile 3, 0.5-kg weight loss to 0.6-kg weight gain). Researchers followed patients from baseline to fibrosis progression or last visit, calculated as person-years, and used the aspartate aminotransferase to platelet ratio index (APRI) to measure outcomes. They defined body mass index based on criteria specific to Asian populations, with underweight categorized as less than 18.5 kg/m^2, normal weight as 18.5-23 kg/m^2, overweight as 23-25 kg/m^2, and obese as at least 25 kg/m^2.

"Our findings from mostly asymptomatic, relatively young individuals with ultrasonographically detected steatosis, possibly reflecting low-risk NAFLD patients, are less likely to be affected by survivor bias and biases related to comorbidities, compared with previous findings from cohorts of high-risk groups that underwent liver biopsy," Seungho Ryu, MD, PhD, from Kangbuk Samsung Hospital in Seoul, South Korea, and colleagues wrote in the study.

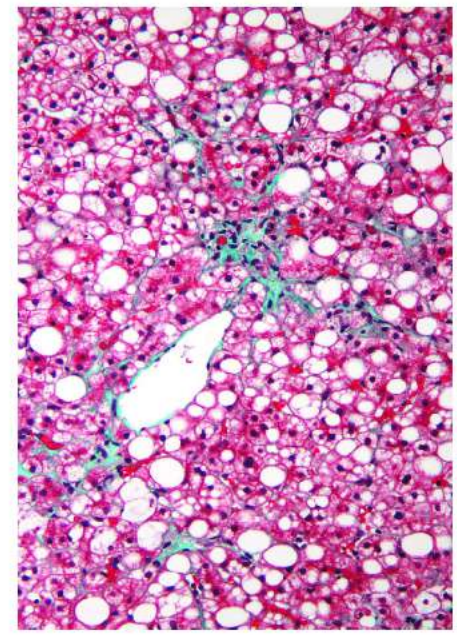
There were 5,454 participants who progressed from a low APRI to an intermediate or high APRI within 275,451.5 person-years, researchers said. Compared with the stable-weight group, hazard ratios for APRI progression in the first weight-change quintile were 0.68 (95% confidence interval, 0.62-0.74) and 0.86 in the second weight-change quintile (95% CI, 0.78-0.94). In the weight-gain groups, an increase in weight was associated with APRI progression in the fourth quintile (HR, 1.17; 95% CI, 1.07-1.28) and fifth quintile (HR, 1.71; 95% CI, 1.58-1.85) groups.

After multivariable adjustment, there was an increase in APRI progression among patients with BMIs between 23 and 24.9 kg/m^2 (HR, 1.13; 95% CI, 1.02-1.26), between 25 and 29.9 kg/m^2 (HR, 1.41; 95% CI, 1.28-1.55), and greater than or equal to 30 kg/m^2 (HR, 2.09; 95% CI, 1.86-2.36) compared with patients with a BMI between 18.5 and 22.9 kg/m^2.

Limitations of the study included the use of ultrasonography in place of liver biopsy for diagnosing NAFLD and the use of APRI to predict fibrosis in individuals with NAFLD, researchers said.

"APRI has demonstrated a reasonable utility as a noninvasive method for the prediction of histologically confirmed advanced fibrosis," Dr. Ryu and colleagues wrote. "Nonetheless, we acknowledge that there is no currently available longitudinal data to support the use of worsening noninvasive fibrosis markers as an indicator of histological progression of fibrosis stage over time."

Other limitations included the study's retrospective design, lack of availability of medication use and dietary intake, and lack of generalization based on a young, healthy population of mostly Korean employees who were employed by companies or local government. However, researchers said clinicians should encourage their patients with NAFLD to maintain a healthy weight to avoid progression of fibrosis.



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SOURCE: Kim Y et al. Clin Gastroenterol Hepatol. 2018. doi: 10.1016/j.cgh.2018.07.006.

FMT suggests IBS efficacy in small, randomized studies

BY MITCHEL L. ZOLER
MDedge News

REPORTING FROM DDW 2018

WASHINGTON – Fecal microbiome transplantation (FMT) showed evidence for significantly improving symptoms in some patients with irritable bowel syndrome (IBS) with predominant diarrhea in two small, independent, randomized controlled studies.

In the more positive of the two studies, patients with "bloating-predominant" IBS received a freshly prepared FMT from either a selected donor or from their own stool as a placebo control. After 12 weeks, the percentage of patients reporting clinically meaningful improvements in both abdominal bloating and IBS symptoms was roughly twice as high, about 56%, among the 43 actively treated patients as the rate in 19 control patients (26%), Tom Holvoet, MD, said at Digestive Disease Week.®

Further follow-up of 22 patients who had significant improvement of their IBS symptoms at 12 weeks after treatment showed that, 1 year later, 6 of the 22 (27%) maintained their improved state while the other 73% of patients relapsed, suggesting that retreatment may be necessary for many, said Dr. Holvoet, a gastroenterologist at Ghent (Belgium) University. Five of the six patients who showed a prolonged response had received a donor FMT, while the sixth patient was from the control group.

"I think some patients would be willing to have multiple treatments," Dr. Holvoet said in an interview. "You need to be highly motivated to undergo this treatment, and if they see an effect they'll be motivated for retreatment," he predicted.

The single-center study enrolled patients 18-75 years old with refractory IBS, based on the Rome III criteria, with intermittent diarrhea and severe bloating. Each patient received a single FMT. Patients in the active-treatment arm received their FMT from either of two donors selected for their "rich microbial diversity," and demonstrated efficacy in an earlier pilot study with 12 patients (Gut. 2017 May;66[5]:980-2). In addition to a higher rate of improvement of symptoms, the donor FMT also led to a significantly better improvement in IBS-related quality of life. Preliminary analysis of the intestinal microbiome profile of patients in the study suggested that specific changes to the microbiome were linked with treatment success.

Dr. Holvoet highlighted that more research is needed to identify ideal patients to treat this way, and to simplify and streamline the FMT process.

Results from the second study failed to show a statistically significant benefit from FMT, compared with placebo, for the primary endpoint, but it did show benefit in one secondary endpoint.

This study enrolled 48 patients 19-65 years old with moderate to severe, diarrhea-predominant IBS, based on the Rome III definitions, at any of three U.S. centers. The researchers randomized patients to either immediate treatment for 3 days with an encapsulated, frozen fecal preparation obtained from the OpenBiome stool bank or placebo capsules. After 12 weeks, the average change from baseline in the IBS–Symptom Severity Score (SSS), the study's primary endpoint, was virtually identical in both arms of the study. In both treatment groups the average baseline IBS-SSS was nearly 300, and in both treatment groups the SSS dropped sharply after 1 week into the study and then remained stable at this lower level in both groups during the next 11 weeks.

Patients then underwent a second round of treatment in a crossover design. During a second 12 weeks of follow-up the average IBS-SSS remained steady among the patients who received placebo as their second treatment, but the patients who received active treatment as their second dose showed a further significant decline in their SSS, so that after the second 12-week follow-up the average score was 76 points lower in patients who recently had active treatment than those who recently received placebo, a statistically significant difference, reported Lawrence J. Brandt, MD, AGAF, professor of medicine and surgery at Albert Einstein College of Medicine in New York.

The 12 patients in the study who had postinfection IBS showed the most dramatic reduction from baseline in their IBS-SSS 12 weeks after active treatment, compared with placebo.

Dr. Holvoet and Dr. Brandt had no disclosures.

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SOURCE: Holvoet T et al. DDW 2018, Presentation 617; Aroniadis OC et al. DDW 2018, Presentation 742.

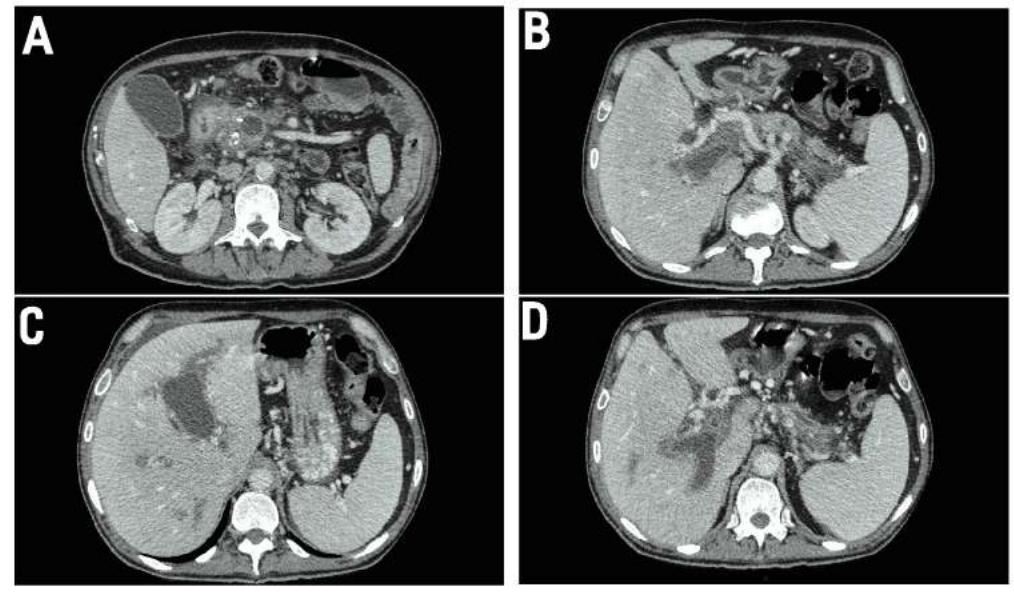
CLINICAL CHALLENGES AND IMAGES

What is your diagnosis?

By Maxime Ronot, MD, Wassim Allaham, MD, and Matthieu Lagadec, MD. Published previously in Gastroenterology (2016;151[5]:817-8).

A 51-year-old man with a history of chronic pancreatitis presented with fatigue, weight loss, and right abdominal pain. He reported excessive alcohol consumption (>200 g of alcohol per day during the past 35 years), active tobacco smoking (70 pack-years), and diabetes mellitus treated by insulin therapy. He had suffered from recurrent epigastric pain, left unexplored, for several weeks. Abdominal examination revealed no anomaly. Laboratory test results showed serum lipase 146 U/L (normal, <78), alkaline phosphatase 477 U/L (normal, <130), gamma-glutamyl transpeptidase 503 U/L (normal, <55), albumin 23 g/L (normal, 40-49), and prealbumin 0.11 g/L (normal, 0.22-0.39).

Contrast-enhanced computed tomography scanning showed features of chronic pancreatitis including pancreatic atrophy, parenchymal calcifications, marked peripancreatic fat stranding, and cephalic hypoattenuating well-delineated collection (Figure A). There was a chronic obstruction of the portal vein that was surrounded by numerous tortuous venous channels (Figure B).



The entire intrahepatic portal branches were occluded, the right and left portal branches showed marked dilatation with a lumen filled with fluid-like material (mean density, 18 Hounsfield units), and no contrast uptake was indicated (Figure C). Portal vein walls were thickened and showed contrast enhancement (Figure D). The superior mesenteric vein was also thrombosed, whereas the splenic vein remained patent. Bile ducts were unnoticeable.

Ultrasound-guided transhepatic puncture of the left portal branch was performed and allowed for the aspiration of a brown fluid. Analysis showed lipase 89,990 UI/dL and amylase 43,125 UI/dL. The patient was treated by parenteral nutrition, anticoagulation therapy, and somatostatin analogues. The patient is doing well at the 6-month follow-up.

The diagnosis is on page 23.

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Researchers find antigen for autoimmune pancreatitis

BY JIM KLING
MDedge News

Researchers have identified laminin 511 as a novel antigen in autoimmune pancreatitis (AIP). A truncated form of the antigen was found in about half of human patients, but fewer than 2% of controls, and mice that were immunized with the antigen responded with induced antibodies and suffered pancreatic injury.

Laminin 511 plays a key role in cell–extracellular matrix (ECM) adhesion in pancreatic tissue. The results, published in Science Translational Medicine, could improve the biologic understanding of AIP and could potentially be a useful diagnostic marker for the disease.

Some autoantibodies are known to be associated with AIP, but the seropositive frequency is low among patients.

The researchers previously demonstrated that injecting IgG from AIP patients into neonatal mice led to pancreatic injury. The IgG was bound to the basement membrane of the pancreatic acini, suggesting the presence of autoantibodies that recognize an antigen in the ECM.

The researchers then screened previously known proteins from the pancreatic ECM against sera from AIP patients, performing Western blot analyses and immunosorbent column chromatography with human and mouse pancreas extracts, and AIP patient IgG. But this approach yielded no results.

The team then conducted an enzyme-linked immunosorbent assay using known pancreatic ECM proteins, which included the laminin subunits 511-FL, 521-FL, 511-E8, 521-E8, 111-EI, 211-E8, and 332-E8. The E8 designates a truncated protein produced by pancreatic elastase that contains the integrin-binding site.

That experiment revealed that 511-E8 is a consistent autoantigen, and a survey of AIP patients found that 26 of 51 (51.0%) had autoantibodies against 511-E8, compared with just 2 of 122 (1.6%) of controls (*P* less than .001). Further immunohistochemistry studies confirmed that patient IgG binds to laminin in pancreatic tissue.

When the researchers injected 511-E8, 511-FL, 521-FL, or ovalbumin into 8-week-old mice, and then again after 28 days and 56 days, only those who received 511-E8 showed evidence of pancreatic injury 28 days after the final immunization. The mice generated autoantibodies to 511-E8 but not ovalbumin.

The findings may have clinical significance. Patients with antibodies to laminin 511-E8 had a lower frequency of malignancies (0% vs. 32%; *P* =.0017) and allergic diseases (12% vs. 48%; *P* =.0043) than patients with no laminin 511-E8 antibodies.

The study was funded by the Japan Society for the Promotion of Science; the Japanese Ministry of Health, Labour, and Welfare; the Practical Research Project for Rare/Intractable Diseases Grant; the Agency for Medical Research and Development; and the Takeda Science Foundation. One of the authors has filed a patent related to the study results.

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SOURCE: Shiokawa M et al. Sci Transl Med. 2018 Aug 8. doi: 10.1126/scitranslmed.aaq0997.

ED visits up for acute pancreatitis linked to younger age, alcohol, chronic disease

BY ANDREW D. BOWSER
MDedge News

The number of U.S. emergency department visits for acute pancreatitis associated with alcohol abuse, chronic pancreatitis history, and younger age was on the rise in recent years, an analysis of a nationally representative database has suggested.

AGA Resource
Help your patients better understand pancreatitis and available tests and treatments by using AGA patient education materials, https://www.gastro.org/practice-guidance/gi-patient-center/topic/pancreatitis.

Meanwhile, hospital admissions and length of stay dropped, but ED and inpatient charges increased, according to the analysis by Sushil K. Garg, MD, of the division of gastroenterology and hepatology at the Mayo Clinic, Rochester, Minn., and his coauthors.

"This study identifies important patient populations, specifically young patients with alcohol abuse, to target in order to develop programs to assist in reduction of ED utilization for acute pancreatitis," Dr. Garg and his colleagues reported in the Journal of Clinical Gastroenterology.

The retrospective analysis was focused on nearly 2.2 million ED visits during 2006-2012 in the National Emergency Department Sample (NEDS) database. The cohort was limited to adults at least 18 years of age with a primary diagnosis of acute pancreatitis.

Overall, there was a nonsignificant 5.5% increase in visits per 10,000 U.S. population during 2006-2012, the researchers found. However, the total number of ED visits in this sample increased significantly – from 292,902 in 2006 to a peak of 326,376, an average rate of increase of 7,213 visits per year (*P* = .0086), according to the report.

Younger patients had a significant increase in the number of pancreatitis-related ED visits over the study period, while older patients had a significant decrease, according to investigators. Visits were up 9.2% for patients aged 18-44 years and 8.6% for those aged 45-64 but down 13.4% for patients aged 65-84 years and 20.1% for those aged 85 years or older.

The incidence of visits secondary to biliary disease was virtually flat over time, Dr. Garg and his coinvestigators found when looking at visits grouped by the most common presenting etiologies. By contrast, there were significant increases in visits for acute pancreatitis associated with alcohol abuse or chronic pancreatitis.

Specifically, acute pancreatitis associated with biliary disease averaged 20.7% of yearly pancreatitis-related ED visits and did not significantly change over time, the researchers reported.

By contrast, acute pancreatitis associated with alcohol abuse, which accounted for 24.1% of visits on average, increased by 15.9% over the study period, an increase driven by an increase among age groups younger than 65 years.

Acute pancreatitis associated with chronic pancreatitis, which made up 11.5% of visits on average, increased "substantially" in all age groups, according to study authors, with the largest increase in the group aged 45-64 years. Overall, the percentage increase over 7 years was 59.5%.

Rates of hospitalization decreased significantly over time, from 76.2% in 2006 to 72.7% in 2012 (*P* = .0026), and likewise, the length of stay dropped from 5.36 to 4.64 days (*P* = .0001), according to the analysis.

Inpatient charges, adjusted for inflation and expressed in 2012 dollars, increased from $32,130.63 to $34,652.00 (*P* = .0011), an average rate of increase of $489/year.

KATARZYNA BIALASIEWICZ/THINKSTOCK

Predictors of hospitalization included age older than 84 years, alcohol use, smoking, and a Charlson comorbidity score of 1 or greater, according to the results of a multivariate regression analysis.

"Factors which may place patients at higher risk for severe or complicated acute pancreatitis requiring admission, such as obesity, alcohol use, and increasing age, are identified and should be explored in further studies and potentially targeted to improve ED and inpatient care," Dr. Garg and his coauthors said.

Dr. Garg and his coauthors had no disclosures related to the study.

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SOURCE: Garg SK et al. J Clin Gastroenterol. 2018 Apr 6. doi: 10.1097/MCG.0000000000001030.

What are best practices?

Seeding *from page 1*

be avoided in all patients with oropharyngeal or esophageal cancer," the clinical practice update states. The authors cite multiple studies linking the pull-through technique to metastasis.

Clinicians also should avoid fine-needle aspiration (FNA) of primary hilar cholangiocarcinomas, especially in patients who are surgical or transplant candidates, wrote Ferga C. Gleeson, MB, BCh, and her associates at M.D. Anderson Cancer Center, Houston. The report is in the September issue of Clinical Gastroenterology and Hepatology (doi: 10.1016/j.cgh.2018.05.014).

For patients with suspected pancreatic cancer, the clinical practice update recommends endoscopic ultrasound (EUS)–guided FNA "in any site within the gland when a confirmatory diagnosis of cancer would alter patient management." The authors also emphasize promptly closing iatrogenic perforations during endoscopic mucosal resection and endoscopic submucosal dissection and practicing nonexposure techniques during endoscopic resection of subepithelial lesions.

For patients with cholangiocarcinoma, primary tumor FNA is controversial because it can be the sole means of cancer diagnosis but also significantly increases the risk of peritoneal metastasis, especially in the setting of larger tumor size, thicker needles, multiple passes, high-grade tumors, and scanty normal tissue along the needle tract, the experts note. Because FNA "may render a patient with cholangiocarcinoma ineligible for entry into a liver transplantation protocol," it is "best to avoid" or at least discuss with a transplant hepatologist, they add.

However, EUS is appropriate when evaluating suspicious lymphadenopathy in liver transplantation candidates with cholangiocarcinoma, they note. This is because imaging techniques have inadequate sensitivity and a positive EUS result would preclude unnecessary neoadjuvant chemoradiation and staging laparotomy. If FNA is negative, patients do require staging laparotomy to verify the absence of nodal disease before transplantation, according to the clinical practice update.

Endoscopic mucosal and submucosal resection are valuable treatment options for esophageal, gastric, and colonic dysplasia and early carcinoma, but they also can lead to unintended gastrointestinal perforation. In past studies, rates of iatrogenic perforation were 1% when patients underwent endoscopic mucosal resection and 5% when they underwent submucosal resection. For patients with any stage of gastric cancer, an accidental perforation can seed the peritoneum with cancer cells from the contents of the stomach. Contact with a primary tumor also can cause shedding of tumor cells that can enter the peritoneal cavity through a perforation. Although most of these cases do not have clinically significant outcomes, perforations need to be promptly closed and should be avoided, if at all possible, during endoscopic full-thickness resections, the experts wrote.

They recommend using nonexposure techniques while resecting subepithelial tumors and call for more safety studies of endoscopic submucosal dissection of malignancies and endoscopic full-thickness resection of subepithelial lesions. "These studies should focus on individual reports or case series of peritoneal or mediastinal examination during surgery following failed resection of these lesions," the authors concluded.

Dr. Gleeson and her associates disclosed no funding sources and reported having no conflicts of interest.

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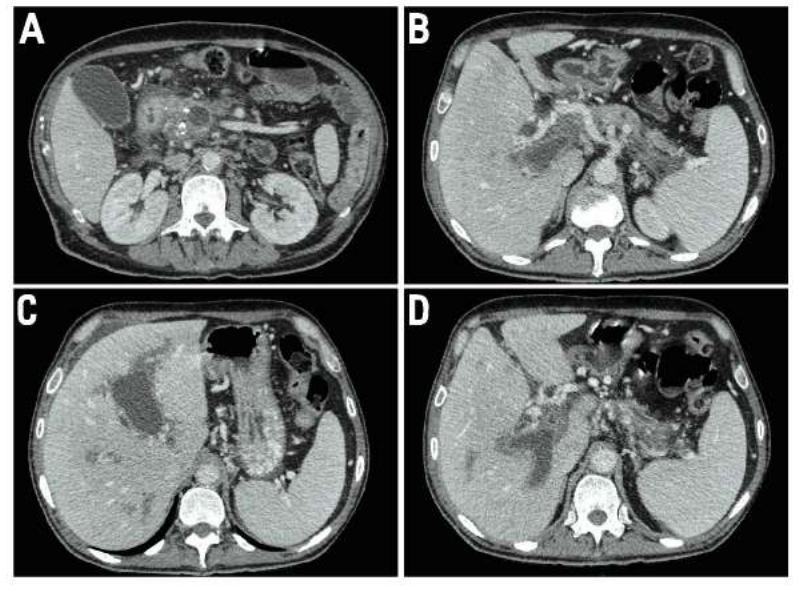
SOURCE: Gleeson FC et al. Clin Gastroenterol Hepatol. 2018 May 17. doi:

CLINICAL CHALLENGES AND IMAGES

The diagnosis

Answer to "What is your diagnosis?" on page 20: Endovascular walled-off pancreatic necrosis complicating a pancreatic duct–portal vein fistula

Pancreatic fistula occurs primarily as a result of abdominal trauma, pancreatic surgery, or disruption of the pancreatic duct. In the vast majority of the cases, the latter is encountered in the context of chronic pancreatitis, and results in chronic pancreatic or peripancreatic fluid or necrotic collections. Rarely, such ductal disruption leads to a direct communication between the ruptured duct and the portal vein lumen. Such pancreas–portal venous fistulas are extremely rare, with less than 20 cases reported in published literature.[1] The location of the fistula is within the head of the pancreas in most cases, and it is associated with intrapancreatic necrotic collection in close proximity to the portal vein, as in the present case. The intravascular flow of pancreatic enzymes leads to local and progressively extensive portal vein thrombosis. Importantly, most portal vein thromboses in the context of acute or chronic pancreatitis do not result from pancreas–portal venous fistula, and are explained by local vascular compression by the inflammatory pancreatic head, and acquired coagulation abnormalities owing to the pancreatitis. In case of fistula, the resulting high blood level of the pancreatic enzymes may lead to a range of clinical presentations, from vague abdominal pain to disseminated fat necrosis. Painful erythematous lesions on the lower extremities and arthritis have also been described. The present case is an exceptional complication of pancreatic duct–portal vein fistula, with endovascular organization of walled-off pancreatic necrosis.[2] The direct visualization of the fistula is difficult, endoscopic retrograde or, more frequently, magnetic resonance cholangiopancreatography being the most useful technique.[3]



AGA Institute

Ultrasound imaging can be useful by showing the heterogeneous yet hypoechoic content of the portal venous system. Percutaneous transhepatic puncture has also been described, and is performed, as in our case, to obtain fluid sample and to perform evacuation of fluid/drainage if necessary. Percutaneous puncture may also provide precise extension of the portal venous invasion. The management of patients with pancreatic–portal vein fistula is poorly codified and relies on individual clinical and imaging analysis. Early surgical intervention has been described in patients with disseminated fat necrosis to limit morbidity and prevent mortality. Later in the evolution of the disease, surgery can be performed if the fistula remains active to alleviate the patient's symptoms and prevent future complications. Finally, conservative treatment can be proposed in selected patients with dried up fistula, as in the present report.

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THE FIRST AND ONLY ORAL JAK INHIBITOR APPROVED FOR UC[1,2]

NOW APPROVED FOR THE TREATMENT OF ADULTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS[2]

JAK=Janus kinase; UC=ulcerative colitis.

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XELJANZ®
(tofacitinib)
5 mg and 10 mg tablets

INDICATION

- XELJANZ (tofacitinib) is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC).
- Limitations of Use: Use of XELJANZ in combination with biologic therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

IMPORTANT SAFETY INFORMATION

SERIOUS INFECTIONS

Patients treated with XELJANZ/XELJANZ XR are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants, such as methotrexate or corticosteroids.

If a serious infection develops, interrupt XELJANZ/XELJANZ XR until the infection is controlled.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before XELJANZ/XELJANZ XR use and during therapy. Treatment for latent infection should be initiated prior to XELJANZ/XELJANZ XR use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

The most common serious infections reported with XELJANZ included pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Avoid use of XELJANZ/XELJANZ XR in patients with an active, serious infection, including localized infections, or with chronic or recurrent infection.

In the UC population, XELJANZ 10 mg twice daily was associated with greater risk of serious infections compared to 5 mg twice daily. Opportunistic herpes zoster infections (including meningoencephalitis, ophthalmologic, and disseminated cutaneous) were seen in patients who were treated with XELJANZ 10 mg twice daily.

The risks and benefits of treatment with XELJANZ/XELJANZ XR should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection, or those who have lived or traveled in areas of endemic TB or mycoses. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ/XELJANZ XR, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Caution is also recommended in patients with a history of chronic lung disease, or in those who develop interstitial lung disease, as they may be more prone to infection.

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with XELJANZ. Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications.

Consider the risks and benefits of XELJANZ/XELJANZ XR treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ/XELJANZ XR in patients who develop a malignancy.

Malignancies (including solid cancers and lymphomas) were observed more often in patients treated with XELJANZ 10 mg twice daily dosing in the UC long-term extension study.

Other malignancies were observed in clinical studies and the post-marketing setting including, but not limited to, lung cancer, breast cancer, melanoma, prostate cancer, and pancreatic cancer. NMSCs have been reported in patients treated with XELJANZ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer. In the UC population, treatment with XELJANZ 10 mg twice daily was associated with greater risk of NMSC.

Please see additional Important Safety Information and brief summary of full Prescribing Information, including **BOXED WARNING**, on the following pages. For current full Prescribing Information, please visit XELJANZPI.com.

IMPORTANT SAFETY INFORMATION (cont'd)

GASTROINTESTINAL PERFORATIONS

Gastrointestinal perforations have been reported in XELJANZ clinical trials, although the role of JAK inhibition is not known. In these studies, many patients with rheumatoid arthritis were receiving background therapy with Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). There was no discernable difference in frequency of gastrointestinal perforation between the placebo and the XELJANZ arms in clinical trials of patients with UC, and many of them were receiving background corticosteroids. XELJANZ/XELJANZ XR should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis or taking NSAIDs).

LABORATORY ABNORMALITIES

Lymphocyte Abnormalities: Treatment with XELJANZ was associated with initial lymphocytosis at one month of exposure followed by a gradual decrease in mean lymphocyte counts. Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with a count less than 500 cells/mm^3. In patients who develop a confirmed absolute lymphocyte count less than 500 cells/mm^3, treatment with XELJANZ/XELJANZ XR is not recommended. Risk of infection may be higher with increasing degrees of lymphopenia and consideration should be given to lymphocyte counts when assessing individual patient risk of infection. Monitor lymphocyte counts at baseline and every 3 months thereafter.

Neutropenia: Treatment with XELJANZ was associated with an increased incidence of neutropenia (less than 2000 cells/mm^3) compared to placebo. Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with an ANC less than 1000 cells/mm^3. For patients who develop a persistent ANC of 500-1000 cells/mm^3, interrupt XELJANZ/XELJANZ XR dosing until ANC is greater than or equal to 1000 cells/mm^3. In patients who develop an ANC less than 500 cells/mm^3, treatment with XELJANZ/XELJANZ XR is not recommended. Monitor neutrophil counts at baseline and after 4-8 weeks of treatment and every 3 months thereafter.

Anemia: Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with a hemoglobin level less than 9 g/dL. Treatment with XELJANZ/XELJANZ XR should be interrupted in patients who develop hemoglobin levels less than 8 g/dL or whose hemoglobin level drops greater than 2 g/dL on treatment. Monitor hemoglobin at baseline and after 4-8 weeks of treatment and every 3 months thereafter.

Liver Enzyme Elevations: Treatment with XELJANZ was associated with an increased incidence of liver enzyme elevation compared to placebo. Most of these abnormalities occurred in studies with background DMARD (primarily methotrexate) therapy. If drug-induced liver injury is suspected, the administration of XELJANZ/XELJANZ XR should be interrupted until this diagnosis has been excluded. Routine monitoring of liver tests and prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury.

Lipid Elevations: Treatment with XELJANZ was associated with dose-dependent increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Maximum effects were generally observed within 6 weeks. There were no clinically relevant changes in LDL/HDL cholesterol ratios. Manage patients with hyperlipidemia according to clinical guidelines. Assessment of lipid parameters should be performed approximately 4-8 weeks following initiation of XELJANZ/XELJANZ XR therapy.

VACCINATIONS

Avoid use of live vaccines concurrently with XELJANZ/XELJANZ XR. The interval between live vaccinations and initiation of tofacitinib therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. Update immunizations in agreement with current immunization guidelines prior to initiating XELJANZ/XELJANZ XR therapy.

PATIENTS WITH GASTROINTESTINAL NARROWING

Caution should be used when administering XELJANZ XR to patients with pre-existing severe gastrointestinal narrowing. There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs utilizing a non-deformable extended release formulation.

HEPATIC and RENAL IMPAIRMENT

Use of XELJANZ/XELJANZ XR in patients with severe hepatic impairment is not recommended.

For patients with moderate hepatic impairment or with moderate or severe renal impairment taking XELJANZ 5 mg twice daily, reduce to XELJANZ 5 mg once daily.

For UC patients with moderate hepatic impairment or with moderate or severe renal impairment taking XELJANZ 10 mg twice daily, reduce to XELJANZ 5 mg twice daily.

ADVERSE REACTIONS

The most common serious adverse reactions were serious infections. The most commonly reported adverse reactions during the first 3 months in controlled clinical trials in patients with rheumatoid arthritis (RA) with XELJANZ 5 mg twice daily and placebo, respectively, (occurring in greater than or equal to 2% of patients treated with XELJANZ with or without DMARDs) were upper respiratory tract infection, nasopharyngitis, diarrhea, headache, and hypertension. The safety profile observed in patients with active psoriatic arthritis treated with XELJANZ was consistent with the safety profile observed in RA patients.

Adverse reactions reported in ≥5% of patients treated with either 5 mg or 10 mg twice daily of XELJANZ and ≥1% greater than reported in patients receiving placebo in either the induction or maintenance clinical trials for ulcerative colitis were: nasopharyngitis, elevated cholesterol levels, headache, upper respiratory tract infection, increased blood creatine phosphokinase, rash, diarrhea, and herpes zoster.

USE IN PREGNANCY

Available data with XELJANZ/XELJANZ XR use in pregnant women are insufficient to establish a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the mother and the fetus associated with rheumatoid arthritis and UC in pregnancy. In animal studies, tofacitinib at 6.3 times the maximum recommended dose of 10 mg twice daily demonstrated adverse embryo-fetal findings. The relevance of these findings to women of childbearing potential is uncertain. Consider pregnancy planning and prevention for females of reproductive potential.

Please see additional Important Safety Information on the previous page and brief summary of full Prescribing Information, including **BOXED WARNING**, on the following pages. For current full Prescribing Information, please visit XELJANZPI.com.

References: 1. Data on file. Pfizer Inc, New York, NY. **2.** XELJANZ [prescribing information]. New York, NY: Pfizer Inc; May 2018.

XELJANZ® (tofacitinib)/XELJANZ® XR (tofacitinib)

BRIEF SUMMARY OF PRESCRIBING INFORMATION. SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with XELJANZ/XELJANZ XR are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt XELJANZ/XELJANZ XR until the infection is controlled.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before XELJANZ/XELJANZ XR use and during therapy. Treatment for latent infection should be initiated prior to XELJANZ/XELJANZ XR use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with XELJANZ/XELJANZ XR should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ/XELJANZ XR, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with XELJANZ. Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications.

INDICATIONS AND USAGE

Rheumatoid Arthritis

XELJANZ/XELJANZ XR is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs).

- Limitations of Use: Use of XELJANZ/XELJANZ XR in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Psoriatic Arthritis

XELJANZ/XELJANZ XR is indicated for the treatment of adult patients with active psoriatic arthritis who have had an inadequate response or intolerance to methotrexate or other disease modifying antirheumatic drugs (DMARDs).

- Limitations of Use: Use of XELJANZ/XELJANZ XR in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Ulcerative Colitis

XELJANZ is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC).

- Limitations of Use: Use of XELJANZ in combination with biological therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Serious Infections Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving XELJANZ. The most common serious infections reported with XELJANZ included pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Among opportunistic infections, tuberculosis and other mycobacterial infections, cryptococcosis, histoplasmosis, esophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, cytomegalovirus infections, BK virus infection, and listeriosis were reported with XELJANZ. Some patients have presented with disseminated rather than localized disease, and were often taking concomitant immunomodulating agents such as methotrexate or corticosteroids.

In the UC population, XELJANZ treatment with 10 mg twice daily was associated with greater risk of serious infections compared to 5 mg twice daily. Additionally, opportunistic herpes zoster infections (including meningoencephalitis, ophthalmologic, and disseminated cutaneous) were seen in patients who were treated with XELJANZ 10 mg twice daily.

Other serious infections that were not reported in clinical studies may also occur (e.g., coccidioidomycosis).

Avoid use of XELJANZ/XELJANZ XR in patients with an active, serious infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating XELJANZ/XELJANZ XR in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ/XELJANZ XR. XELJANZ/XELJANZ XR should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with XELJANZ/XELJANZ XR should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

Caution is also recommended in patients with a history of chronic lung disease, or in those who develop interstitial lung disease, as they may be more prone to infections.

Risk of infection may be higher with increasing degrees of lymphopenia and consideration should be given to lymphocyte counts when assessing individual patient risk of infection. Discontinuation and monitoring criteria for lymphopenia are recommended.

Tuberculosis Patients should be evaluated and tested for latent or active infection prior to and per applicable guidelines during administration of XELJANZ/XELJANZ XR.

Anti-tuberculosis therapy should also be considered prior to administration of XELJANZ/XELJANZ XR in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but who have risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision about whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Patients should be closely monitored for the development of signs and symptoms of tuberculosis, including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before administering XELJANZ/XELJANZ XR.

Viral Reactivation Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were observed in clinical studies with XELJANZ. The impact of XELJANZ/XELJANZ XR on chronic viral hepatitis reactivation is unknown. Patients who screened positive for hepatitis B or C were excluded from clinical trials. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with XELJANZ/XELJANZ XR. The risk of herpes zoster is increased in patients treated with XELJANZ/XELJANZ XR and appears to be higher in patients treated with XELJANZ in Japan and Korea.

Malignancy and Lymphoproliferative Disorders Consider the risks and benefits of XELJANZ/XELJANZ XR treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ/XELJANZ XR in patients who develop a malignancy. Malignancies were observed in clinical studies of XELJANZ.

In the seven controlled rheumatoid arthritis clinical studies, 11 solid cancers and one lymphoma were diagnosed in 3328 patients receiving XELJANZ

with or without DMARD, compared to 0 solid cancers and 0 lymphomas in 809 patients in the placebo with or without DMARD group during the first 12 months of exposure. Lymphomas and solid cancers have also been observed in the long-term extension studies in rheumatoid arthritis patients treated with XELJANZ.

During the 2 PsA controlled clinical studies there were 3 malignancies (excluding NMSC) in 474 patients receiving XELJANZ plus nonbiologic DMARD (6 to 12 months exposure) compared with 0 malignancies in 236 patients in the placebo plus nonbiologic DMARD group (3 months exposure) and 0 malignancies in 106 patients in the adalimumab plus nonbiologic DMARD group (12 months exposure). No lymphomas were reported. Malignancies have also been observed in the long-term extension study in psoriatic arthritis patients treated with XELJANZ.

During the UC controlled clinical studies (8-week induction and 52-week maintenance studies), which included 1220 patients, 0 cases of solid cancer or lymphoma were observed in XELJANZ-treated patients. In the long-term extension study, malignancies (including solid cancers and lymphomas) were observed more often in patients treated with XELJANZ 10 mg twice daily.

In Phase 2B, controlled dose-ranging trials in *de-novo* renal transplant patients, all of whom received induction therapy with basiliximab, high-dose corticosteroids, and mycophenolic acid products, Epstein Barr Virus-associated post-transplant lymphoproliferative disorder was observed in 5 out of 218 patients treated with XELJANZ (2.3%) compared to 0 out of 111 patients treated with cyclosporine.

Other malignancies were observed in clinical studies and the post-marketing setting, including, but not limited to, lung cancer, breast cancer, melanoma, prostate cancer, and pancreatic cancer.

Non-Melanoma Skin Cancer Non-melanoma skin cancers (NMSCs) have been reported in patients treated with XELJANZ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer. In the UC population, treatment with XELJANZ 10 mg twice daily was associated with greater risk of NMSC.

Gastrointestinal Perforations Events of gastrointestinal perforation have been reported in clinical studies with XELJANZ, although the role of JAK inhibition in these events is not known. In these studies, many patients with rheumatoid arthritis were receiving background therapy with Nonsteroidal Anti-Inflammatory Drugs (NSAIDs).

There was no discernable difference in frequency of gastrointestinal perforation between the placebo and the XELJANZ arms in clinical trials of patients with UC, and many of them were receiving background corticosteroids.

XELJANZ/XELJANZ XR should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis or taking NSAIDs). Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Serious Infections
- Malignancy and Lymphoproliferative Disorders
- Gastrointestinal Perforations
- Laboratory Abnormalities

Clinical Trials Experience Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not predict the rates observed in a broader patient population in clinical practice.

Rheumatoid Arthritis The clinical studies described in the following sections were conducted using XELJANZ. Although other doses of XELJANZ have been studied, the recommended dose of XELJANZ is 5 mg twice daily.

The recommended dose for XELJANZ XR is 11 mg once daily.

The following data includes two Phase 2 and five Phase 3 double-blind, controlled, multicenter trials. In these trials, patients were randomized to doses of XELJANZ 5 mg twice daily (292 patients) and 10 mg twice daily (306 patients) monotherapy, XELJANZ 5 mg twice daily (1044 patients) and 10 mg twice daily (1043 patients) in combination with DMARDs (including methotrexate) and placebo (809 patients). All seven protocols included provisions for patients taking placebo to receive treatment with XELJANZ at Month 3 or Month 6 either by patient response (based on uncontrolled disease activity) or by design, so that adverse events cannot always be unambiguously attributed to a given treatment. Therefore, some analyses that follow include patients who changed treatment by design or by patient response from placebo to XELJANZ in both the placebo and XELJANZ group of a given interval. Comparisons between placebo and XELJANZ were based on the first 3 months of exposure, and comparisons between XELJANZ 5 mg twice daily and XELJANZ 10 mg twice daily were based on the first 12 months of exposure.

The long-term safety population includes all patients who participated in a double-blind, controlled trial (including earlier development phase studies) and then participated in one of two long-term safety studies. The design of the long-term safety studies allowed for modification of XELJANZ doses according to clinical judgment. This limits the interpretation of the long-term safety data with respect to dose.

The most common serious adverse reactions were serious infections.

The proportion of patients who discontinued treatment due to any adverse reaction during the 0 to 3 months exposure in the double-blind, placebo-controlled trials was 4% for patients taking XELJANZ and 3% for placebo-treated patients.

Overall Infections In the seven controlled trials, during the 0 to 3 months exposure, the overall frequency of infections was 20% and 22% in the 5 mg twice daily and 10 mg twice daily groups, respectively, and 18% in the placebo group.

The most commonly reported infections with XELJANZ were upper respiratory tract infections, nasopharyngitis, and urinary tract infections (4%, 3%, and 2% of patients, respectively).

Serious Infections In the seven controlled trials, during the 0 to 3 months exposure, serious infections were reported in 1 patient (0.5 events per 100 patient-years) who received placebo and 11 patients (1.7 events per 100 patient-years) who received XELJANZ 5 mg or 10 mg twice daily. The rate difference between treatment groups (and the corresponding 95% confidence interval) was 1.1 (-0.4, 2.5) events per 100 patient-years for the combined 5 mg twice daily and 10 mg twice daily XELJANZ group minus placebo.

In the seven controlled trials, during the 0 to 12 months exposure, serious infections were reported in 34 patients (2.7 events per 100 patient-years) who received 5 mg twice daily of XELJANZ and 33 patients (2.7 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was -0.1 (-1.3, 1.2) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ.

The most common serious infections included pneumonia, cellulitis, herpes zoster, and urinary tract infection.

Tuberculosis In the seven controlled trials, during the 0 to 3 months exposure, tuberculosis was not reported in patients who received placebo, 5 mg twice daily of XELJANZ, or 10 mg twice daily of XELJANZ.

In the seven controlled trials, during the 0 to 12 months exposure, tuberculosis was reported in 0 patients who received 5 mg twice daily of XELJANZ and 6 patients (0.5 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was 0.5 (0.1, 0.9) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ.

Cases of disseminated tuberculosis were also reported. The median XELJANZ exposure prior to diagnosis of tuberculosis was 10 months (range from 152 to 960 days).

Opportunistic Infections (excluding tuberculosis) In the seven controlled trials, during the 0 to 3 months exposure, opportunistic infections were not reported in patients who received placebo, 5 mg twice daily of XELJANZ, or 10 mg twice daily of XELJANZ.

In the seven controlled trials, during the 0 to 12 months exposure, opportunistic infections were reported in 4 patients (0.3 events per 100 patient-years) who received 5 mg twice daily of XELJANZ and 4 patients (0.3 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was 0 (-0.5, 0.5) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ.

The median XELJANZ exposure prior to diagnosis of an opportunistic infection was 8 months (range from 41 to 698 days).

Malignancy In the seven controlled trials, during the 0 to 3 months exposure, malignancies

excluding NMSC were reported in 0 patients who received placebo and 2 patients (0.3 events per 100 patient years) who received either XELJANZ 5 mg or 10 mg twice daily. The rate difference between treatment groups (and the corresponding 95% confidence interval) was 0.3 (-0.1, 0.7) events per 100 patient- years for the combined 5 mg and 10 mg twice daily XELJANZ group minus placebo.

In the seven controlled trials, during the 0 to 12 months exposure, malignancies excluding NMSC were reported in 5 patients (0.4 events per 100 patient-years) who received 5 mg twice daily of XELJANZ and 7 patients (0.6 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was 0.2 (-0.4, 0.7) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ. One of these malignancies was a case of lymphoma that occurred during the 0 to 12 month period in a patient treated with XELJANZ 10 mg twice daily.

The most common types of malignancy, including malignancies observed during the long-term extension, were lung and breast cancer, followed by gastric, colorectal, renal cell, prostate cancer, lymphoma, and malignant melanoma.

Laboratory Abnormalities

Lymphopenia In the controlled clinical trials, confirmed decreases in absolute lymphocyte counts below 500 cells/mm^3 occurred in 0.04% of patients for the 5 mg twice daily and 10 mg twice daily XELJANZ groups combined during the first 3 months of exposure.

Confirmed lymphocyte counts less than 500 cells/mm^3 were associated with an increased incidence of treated and serious infections.

Neutropenia In the controlled clinical trials, confirmed decreases in ANC below 1000 cells/mm^3 occurred in 0.07% of patients for the 5 mg twice daily and 10 mg twice daily XELJANZ groups combined during the first 3 months of exposure.

There were no confirmed decreases in ANC below 500 cells/mm^3 observed in any treatment group.

There was no clear relationship between neutropenia and the occurrence of serious infections.

In the long-term safety population, the pattern and incidence of confirmed decreases in ANC remained consistent with what was seen in the controlled clinical trials.

Liver Enzyme Elevations Confirmed increases in liver enzymes greater than 3 times the upper limit of normal (3x ULN) were observed in patients treated with XELJANZ. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as reduction in the dose of concomitant DMARD, interruption of XELJANZ, or reduction in XELJANZ dose, resulted in decrease or normalization of liver enzymes.

In the controlled monotherapy trials (0-3 months), no differences in the incidence of ALT or AST elevations were observed between the placebo, and XELJANZ 5 mg, and 10 mg twice daily groups.

In the controlled background DMARD trials (0-3 months), ALT elevations greater than 3x ULN were observed in 1.0%, 1.3% and 1.2% of patients receiving placebo, 5 mg, and 10 mg twice daily, respectively. In these trials, AST elevations greater than 3x ULN were observed in 0.6%, 0.5% and 0.4% of patients receiving placebo, 5 mg, and 10 mg twice daily, respectively.

One case of drug-induced liver injury was reported in a patient treated with XELJANZ 10 mg twice daily for approximately 2.5 months. The patient developed symptomatic elevations of AST and ALT greater than 3x ULN and bilirubin elevations greater than 2x ULN, which required hospitalizations and a liver biopsy.

Lipid Elevations In the controlled clinical trials, dose-related elevations in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) were observed at one month of exposure and remained stable thereafter. Changes in lipid parameters during the first 3 months of exposure in the controlled clinical trials are summarized below:

- Mean LDL cholesterol increased by 15% in the XELJANZ 5 mg twice daily arm and 19% in the XELJANZ 10 mg twice daily arm.
- Mean HDL cholesterol increased by 10% in the XELJANZ 5 mg twice daily arm and 12% in the XELJANZ 10 mg twice daily arm.
- Mean LDL/HDL ratios were essentially unchanged in XELJANZ-treated patients.

In a controlled clinical trial, elevations in LDL cholesterol and ApoB decreased to pretreatment levels in response to statin therapy.

In the long-term safety population, elevations in lipid parameters remained consistent with what was seen in the controlled clinical trials.

Serum Creatinine Elevations In the controlled clinical trials, dose-related elevations in serum creatinine were observed with XELJANZ treatment. The mean increase in serum creatinine was <0.1 mg/dL in the 12-month pooled safety analysis; however with increasing duration of exposure in the long-term extensions, up to 2% of patients were discontinued from XELJANZ treatment due to the protocol-specified discontinuation criterion of an increase in creatinine by more than 50% of baseline. The clinical significance of the observed serum creatinine elevations is unknown.

Other Adverse Reactions Adverse reactions occurring in 2% or more of patients on 5 mg twice daily or 10 mg twice daily XELJANZ and at least 1% greater than that observed in patients on placebo with or without DMARD are summarized in the table below.

Common Adverse Reactions* in Clinical Trials of XELJANZ for the Treatment of Rheumatoid Arthritis With or Without Concomitant DMARDs (0-3 Months)

Preferred Team	XELJANZ 5 mg Twice Daily N = 1336 (%)	XELJANZ 10 mg Twice Daily** N = 1349 (%)	Placebo N = 809 (%)
Upper respiratory tract infection	4	4	3
Nasopharyngitis	4	3	3
Diarrhea	4	3	2
Headache	4	3	2
Hypertension	2	2	1

N reflects randomized and treated patients from the seven clinical trials.

* reported in ≥2% of patients treated with either dose of XELJANZ and ≥1% greater than that reported for placebo.

** the recommended dose of XELJANZ for the treatment of rheumatoid arthritis is 5 mg twice daily.

Other adverse reactions occurring in controlled and open-label extension studies included:

Blood and lymphatic system disorders: Anemia

Infections and infestations: Diverticulitis

Metabolism and nutrition disorders: Dehydration

Psychiatric disorders: Insomnia

Nervous system disorders: Paresthesia

Respiratory, thoracic and mediastinal disorders: Dyspnea, cough, sinus congestion, interstitial lung disease (cases were limited to patients with rheumatoid arthritis and some were fatal)

Gastrointestinal disorders: Abdominal pain, dyspepsia, vomiting, gastritis, nausea

Hepatobiliary disorders: Hepatic steatosis

Skin and subcutaneous tissue disorders: Rash, erythema, pruritus

Musculoskeletal, connective tissue and bone disorders: Musculoskeletal pain, arthralgia, tendonitis, joint swelling

Neoplasms benign, malignant and unspecified (including cysts and polyps): Non-melanoma skin cancers

General disorders and administration site conditions: Pyrexia, fatigue, peripheral edema

Clinical Experience in Methotrexate-Naïve Patients Study RA-VI was an active-controlled clinical trial in methotrexate-naïve patients. The safety experience in these patients was consistent with Studies RA-I through V.

Psoriatic Arthritis XELJANZ 5 mg twice daily and 10 mg twice daily were studied in 2 double-blind Phase 3 clinical trials in patients with active psoriatic arthritis (PsA).

Study PsA-I (NCT01877668) had a duration of 12 months and enrolled patients who had an inadequate response to a nonbiologic DMARD and who were naïve to treatment with a TNF blocker. Study PsA-I included a 3-month placebo-controlled period and also included adalimumab 40 mg subcutaneously once every 2 weeks for 12 months.

Study PsA-II (NCT01882439) had a duration of 6 months and enrolled patients who had an inadequate response to at least one approved TNF blocker. This clinical trial included a 3-month placebo controlled period.

In these combined Phase 3 clinical trials, 238 patients were randomized and treated with XELJANZ 5 mg twice daily and 236 patients were randomized and treated with XELJANZ 10 mg twice daily. All patients in the clinical trials were required to receive treatment with a stable dose of a nonbiologic DMARD [the majority (79%) received methotrexate]. The study population randomized and treated with XELJANZ (474 patients) included 45 (9.5%) patients aged 65 years or older and 66 (13.9%) patients with diabetes at baseline.

The safety profile observed in patients with active psoriatic arthritis treated with XELJANZ was consistent with the safety profile observed in rheumatoid arthritis patients.

Ulcerative Colitis XELJANZ has been studied in patients with moderately to severely active UC in 4 randomized, double-blind, placebo-controlled trials (UC-I, UC-II, UC-III, and dose ranging UC-V) and an open-label long term extension study (UC-IV).

Adverse reactions reported in ≥5% of patients treated with either 5 mg or 10 mg twice daily of XELJANZ and ≥1% greater than reported in patients receiving placebo in either the induction or maintenance clinical trials were: nasopharyngitis, elevated cholesterol levels, headache, upper respiratory tract infection, increased blood creatine phosphokinase, rash, diarrhea, and herpes zoster.

Induction Trials (Study UC-I, UC-II, and UC-V):
Common adverse reactions reported in ≥2% of patients treated with XELJANZ 10 mg twice daily and ≥1% greater than that reported in patients receiving placebo in the 3 induction trials were: headache, nasopharyngitis, elevated cholesterol levels, acne, increased blood creatine phosphokinase, and pyrexia.

Maintenance Trial (Study UC-III)
Common adverse reactions reported in ≥4% of patients treated with either dose of XELJANZ and ≥1% greater than reported in patients receiving placebo are shown in the table below.

Common Adverse Reactions* in UC Patients during the Maintenance Trial (Study UC-III)

Preferred Term	XELJANZ 5 mg Twice Daily N = 198 (%)	XELJANZ 10 mg Twice Daily N = 196 (%)	Placebo N = 198 (%)
Nasopharyngitis	10	14	6
Elevated cholesterol levels**	5	9	1
Headache	9	3	6
Upper respiratory tract infection	7	6	4
Increased blood creatine phosphokinase	3	7	2
Rash	3	6	4
Diarrhea	2	5	3
Herpes zoster	1	5	1
Gastroenteritis	3	4	3
Anemia	4	2	2
Nausea	1	4	3

* reported in ≥4% of patients treated with either dose of XELJANZ and ≥1% greater than reported for placebo.

** includes hypercholesterolemia, hyperlipidemia, blood cholesterol increased, dyslipidemia, blood triglycerides increased, low density lipoprotein increased, low density lipoprotein abnormal, or lipids increased.

In the long-term extension study, malignancies (including solid cancers, lymphomas and NMSC) were observed more often in patients treated with XELJANZ 10 mg twice daily. Four cases of pulmonary embolism were reported in patients taking XELJANZ 10 mg twice daily, including one fatality in a patient with advanced cancer.

Dose-dependent adverse reactions seen in patients treated with XELJANZ 10 mg twice daily, in comparison to 5 mg twice daily, include the following: herpes zoster infections, serious infections, and NMSC.

DRUG INTERACTIONS

The table below includes drugs with clinically important drug interactions when administered concomitantly with XELJANZ/XELJANZ XR and instructions for preventing or managing them.

Clinical Relevant Interactions Affecting XELJANZ and XELJANZ XR When Coadministered with Other Drugs

Strong CP3A4 Inhibitors (e.g., ketoconazole)	
Clinical Impact	Increased exposure to tofacitinib
Intervention	Dosage adjustment of XELJANZ/ XELJANZ XR is recommended
Moderate CYP3A4 Inhibitors Coadministered with Strong CYP2C19 Inhibitors (e.g., fluconazole)	
Clinical Impact	Increased exposure to tofacitinib
Intervention	Dosage adjustment of XELJANZ/ XELJANZ XR is recommended
Strong CYP3A4 Inducers (e.g., rifampin)	
Clinical Impact	Decreased exposure to tofacitinib and may result in loss of or reduced clinical response
Intervention	Coadministration with XELJANZ/ XELJANZ XR is not recommended
Immunosuppressive Drugs (e.g., azathioprine, tacrolimus, cyclosporine)	
Clinical Impact	Risk of added immunosuppression; coadministration with biologic DMARDs or potent immunosuppressants has not been studied in patients with rheumatoid arthritis, psoriatic arthritis, or UC.
Intervention	Coadministration with XELJANZ/ XELJANZ XR is not recommended

USE IN SPECIFIC POPULATIONS

All information provided in this section is applicable to XELJANZ and XELJANZ XR as they contain the same active ingredient (tofacitinib).

Pregnancy

Pregnancy Exposure Registry There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to XELJANZ/XELJANZ XR during pregnancy. Patients should be encouraged to enroll in the XELJANZ/XELJANZ XR pregnancy registry if they become pregnant. To enroll or obtain information from the registry, patients can call the toll free number 1-877-311-8972.

Risk Summary Available data with XELJANZ/ XELJANZ XR use in pregnant women are insufficient to establish a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the mother and the fetus associated with rheumatoid arthritis and UC in pregnancy *(see Clinical Considerations)*. In animal reproduction studies, fetocidal and teratogenic effects were noted when pregnant rats and rabbits received tofacitinib during the period of organogenesis at exposures multiples of 73-times and 6.3-times the maximum recommended dose of 10 mg twice daily, respectively. Further, in a peri and post-natal study in rats, tofacitinib resulted in reductions in live litter size, postnatal survival, and pup body weights at exposure multiples of approximately 73-times the recommended dose of 5 mg twice daily and approximately 36 times the maximum recommended dose of 10 mg twice daily, respectively *(see Data)*.

The estimated background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risks in the U.S. general population of major birth defects and miscarriages are 2 to 4% and 15 to 20% of clinically recognized pregnancies, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/ Fetal Risk

Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with rheumatoid arthritis or ulcerative colitis. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Data

Animal Data In a rat embryofetal developmental study, in which pregnant rats received tofacitinib during organogenesis, tofacitinib was teratogenic at exposure levels approximately 146 times the recommended dose of 5 mg twice daily, and approximately 73 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 100 mg/kg/day in rats). Teratogenic effects consisted of external and soft tissue malformations of anasarca and membranous ventricular septal defects, respectively; and skeletal malformations or variations (absent cervical arch; bent femur, fibula, humerus, radius, scapula, tibia, and ulna; sternoschisis; absent rib; misshapen femur; branched rib; fused rib; fused sternebra; and hemicentric thoracic centrum). In addition, there was an increase in post-implantation loss, consisting of early and late resorptions, resulting in a reduced number of viable fetuses. Mean fetal body weight was reduced. No developmental toxicity was observed in rats at exposure levels approximately 58 times the recommended dose of 5 mg twice daily, and approximately 29 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 30 mg/kg/day in pregnant rats).

In a rabbit embryofetal developmental study in which pregnant rabbits received tofacitinib during the period of organogenesis, tofacitinib was teratogenic at exposure levels approximately 13 times the recommended dose of 5 mg twice daily, and approximately 6.3 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 30 mg/kg/day in rabbits) in the absence of signs of maternal toxicity. Teratogenic effects included thoracogastroschisis, omphalocele, membranous ventricular septal defects, and cranial/skeletal malformations (microstomia, microphthalmia), mid-line and tail defects. In addition, there was an increase in post-implantation loss associated with late resorptions. No developmental toxicity was observed in rabbits at exposure levels approximately 3 times the recommended dose of 5 mg twice daily, and approximately 1.5 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 10 mg/kg/day in pregnant rabbits).

In a peri- and postnatal development study in pregnant rats that received tofacitinib from gestation day 6 through day 20 of lactation, there were reductions in live litter size, postnatal

survival, and pup body weights at exposure levels approximately 73 times the recommended dose of 5 mg twice daily, and approximately 36 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 50 mg/kg/day in rats). There was no effect on behavioral and learning assessments, sexual maturation or the ability of the F1 generation rats to mate and produce viable F2 generation fetuses in rats at exposure levels approximately 17 times the recommended dose of 5 mg twice daily, and approximately 8.3 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 10 mg/kg/day in rats).

Lactation

Risk Summary There are no data on the presence of tofacitinib in human milk, the effects on a breastfed infant, or the effects on milk production. Tofacitinib is present in the milk of lactating rats *(see Data)*. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Given the serious adverse reactions seen in adults treated with XELJANZ/XELJANZ XR, such as increased risk of serious infections, advise patients that breastfeeding is not recommended during treatment and for at least 18 hours after the last dose of XELJANZ or 36 hours after the last dose of XELJANZ XR (approximately 6 elimination half-lives).

Data
Following administration of tofacitinib to lactating rats, concentrations of tofacitinib in milk over time paralleled those in serum, and were approximately 2 times higher in milk relative to maternal serum at all time points measured.

Females and Males of Reproductive Potential

Contraception
Females In an animal reproduction study, tofacitinib at AUC multiples of 13 times the recommended dose of 5 mg twice daily and 6.3 times the maximum recommended dose of 10 mg twice daily demonstrated adverse embryo-fetal findings. However, there is uncertainty as to how these animal findings relate to females of reproductive potential treated with the recommended clinical dose. Consider pregnancy planning and prevention for females of reproductive potential.

Infertility
Females Based on findings in rats, treatment with XELJANZ/XELJANZ XR may result in reduced fertility in females of reproductive potential. It is not known if this effect is reversible.

Pediatric Use
The safety and effectiveness of XELJANZ/XELJANZ XR in pediatric patients have not been established.

Geriatric Use
Of the 3315 patients who enrolled in rheumatoid arthritis Studies I to V, a total of 505 rheumatoid arthritis patients were 65 years of age and older, including 71 patients 75 years and older. The frequency of serious infection among XELJANZ-treated subjects 65 years of age and older was higher than among those under the age of 65.

Of the 1156 XELJANZ treated patients in the UC program, a total of 77 patients (7%) were 65 years of age or older. The number of patients aged 65 years and older was not sufficient to determine whether they responded differently from younger patients.

As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

Use in Diabetics
As there is a higher incidence of infection in diabetic population in general, caution should be used when treating patients with diabetes.

Renal Impairment
Moderate and Severe Impairment
XELJANZ-treated patients with moderate or severe renal impairment had greater tofacitinib blood concentrations than XELJANZ-treated patients with normal renal function. Therefore, dosage adjustment of XELJANZ is recommended in patients with moderate or severe renal impairment.

- Rheumatoid arthritis and psoriatic arthritis patients with moderate or severe renal impairment receiving XELJANZ XR should switch to XELJANZ and adjust the dosage.

Mild impairment
No dosage adjustment is required in patients with mild renal impairment.

Hepatic Impairment
Severe Impairment
XELJANZ/XELJANZ XR has not been studied in patients with severe hepatic impairment; therefore, use of XELJANZ/XELJANZ XR in patients with severe hepatic impairment is not recommended.

Moderate Impairment
XELJANZ-treated patients with moderate hepatic impairment had greater tofacitinib blood concentration than XELJANZ-treated patients with normal hepatic function. Higher blood concentrations may increase the risk of some adverse reactions. Therefore, dosage adjustment of XELJANZ is recommended in patients with moderate hepatic impairment.

- Rheumatoid arthritis and psoriatic arthritis patients receiving XELJANZ XR should switch to XELJANZ and adjust the dosage.

Mild Impairment
No dosage adjustment of XELJANZ/XELJANZ XR is required in patients with mild hepatic impairment.

Hepatitis B or C Serology
The safety and efficacy of XELJANZ/XELJANZ XR have not been studied in patients with positive hepatitis B virus or hepatitis C virus serology.

OVERDOSAGE
There is no specific antidote for overdose with XELJANZ/XELJANZ XR. In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions.

This brief summary is based on XELJANZ®/XELJANZ® XR (tofacitinib) Prescribing Information LAB-0445-13.0

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PRACTICE MANAGEMENT TOOLBOX:

Patient-reported outcomes in esophageal diseases

BY CRAIG C. REED, MD, MCSR, AND EVAN S. DELLON, MD, MPH

Patients seek medical care for symptoms affecting their quality of life,[1] and this is particularly true of digestive diseases, in which many common conditions are symptom predominant. However, clinician and patient perception of symptoms often conflict,[2] and formalized measurement tools may have a role for optimizing symptom assessment. Patient-reported outcomes (PROs) directly capture patients' health status from their own perspectives and can bridge the divide between patient and provider interpretation. The U.S. Food and Drug Administration (FDA) defines PROs as "any report of the status of a patient's health condition that comes directly from the patient without interpretation of the patient's response by a clinician or anyone else."[3]

For the clinical assessment of esophageal diseases, existing physiologic and structural testing modalities cannot ascertain patient disease perception or measure the impact of symptoms on health care–associated quality of life. In contrast, through capture of patient-centric data, PROs can provide insight into the psychosocial aspects of patient disease perceptions; capture health-related quality of life (HRQL); improve provider understanding; highlight discordance between physiologic, symptom, and HRQL measures; and formalize follow-up evaluation of treatment response.[1,4] Following up symptoms such as dysphagia or heartburn over time in a structured way allows clinically obtained data to be used in pragmatic or comparative effectiveness studies. PROs are now an integral part of the FDA's drug approval process.

In this article, we review the available PROs capturing esophageal symptoms with a focus on dysphagia and heartburn measures that were developed with rigorous methodology; it is beyond the scope of this article to perform a thorough review of all upper gastrointestinal PROs or quality-of-life PROs. We then discuss how esophageal PROs may be incorporated into clinical practice now, as well as opportunities for PRO use in the future.

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Esophageal symptom–specific PROs

The literature pertinent to upper GI and esophageal-specific PROs is heterogeneous, and the development of PROs has been variable in rigor. Two recent systematic reviews identified PROs pertinent to dysphagia and heartburn (Table 1) and both emphasized rigorous measures developed in accordance with FDA guidance.[3]

Patel et al.[5] identified 34 dysphagia-specific PRO measures, of which 10 were rigorously developed (Table 1). The systematic review by Vakil et al.[6] found 15 PRO measures for gastroesophageal reflux disease (GERD) symptoms that underwent psychometric evaluation (Table 1). Of these, five measures were devised according to the developmental steps stipulated by the U.S. FDA and the European Medicines Agency, and each measure has been used as an endpoint for a clinical trial.

Although HRQL measures exist for esophageal symptoms, a thorough discussion of these measures exceeds the scope of this article. The utilization of many HRQL instruments may be problematic because they either may not be disease-specific or they may poorly translate across disease processes. The Northwestern Esophageal Quality of Life instrument, a rigorously developed measure that recently was introduced, addresses these concerns and may be used for a variety of diseases and symptoms affecting the esophagus.[7]

Utilization of esophageal PROs in practice

Before incorporating a PRO into clinical practice, providers must appreciate the construct(s), intent, developmental measurement properties, validation strategies, and responsiveness characteristics associated with the measure.[4] PROs can be symptom and/or condition specific. For example, this could include dysphagia associated with achalasia or eosinophilic esophagitis, postoperative dysphagia from spine surgery, or general dysphagia symptoms regardless of the etiology (Table 1). Intent refers to the context in which a PRO should be used and generally is stratified into three areas: population surveillance, individual patient-clinician interactions, and research studies.[4] A thorough analysis of PRO developmental properties exceeds the scope of this article. However, several key considerations are worth discussing. Each measure should clearly delineate the construct, or outcome, in addition to the population used to create the measure (e.g., patients with achalasia). PROs should be assessed for reliability, construct validity, and content validity. Reliability pertains to the degree in which scores are free from measurement error, the extent to which items (i.e., questions) correlate, and test–retest reliability. Construct validity includes dimensionality (evidence of whether a single or multiple subscales exist in the measure), responsiveness to change (longitudinal validity), and convergent validity (correlation with additional construct-specific measures). Central to the PRO development process is the involvement of patients and content experts (content validity). PRO measures should be readily interpretable, and the handling of missing items should be stipulated. The burden, or time required for administering and scoring the instrument, and the reading level of the PRO need to be considered.[8] In short, a PRO should measure something important to patients, in a way that patients can understand, and in a way that accurately reflects the underlying symptom and disease.

Although PROs traditionally represent a method for gathering data for research, they also should be viewed as a means of improving clinical care. The monitoring of change in a particular construct represents a common application of PROs in clinical practice. This helps quantify the efficacy of an intervention and can provide insight into the comparative effectiveness of alternative therapies. For example, in a patient with an esophageal stricture, a dysphagia-specific measure could be used at baseline before an endoscopy and dilation, in follow-up evaluation after dilation, and then as a monitoring tool to determine when repeat dilation may be needed. Similarly, the Eckardt score has been used commonly to monitor response to achalasia treatments. Clinicians also may use PROs in real time to optimize patient management. The data gathered from PROs may help triage patients into treatment pathways, trigger follow-up appointments, supply patient education prompts, and produce patient and provider alerts.[8] For providers engaging in clinical research, PROs administered at the point of patient intake, whether electronically through a patient portal or in the clinic, provide a means of gathering baseline data.[9] A key question, however, is whether it is practical to use a PRO routinely in the clinic, esophageal function laboratory, or endoscopy suite.

These practical issues include cultivating an environment for PRO utilization, considering the burden of the measure on patients, and utilization of the results in an expedient manner.[9] To promote seamless use of a PRO in clinical work-flows, a multimodal means of collecting PRO data should be arranged. Electronic PROs available through a patient portal, designed with a user-friendly and intuitive interface, facilitate patient completion of PROs. For patients without access to the internet, tablets and/or computer terminals within the office are convenient options. Nurses or clinic staff also could help patients complete a PRO during check-in for clinic, esophageal testing, or endoscopy. The burden a PRO imposes on patients also limits the utility of a measure. For instance, PROs with a small number of questions are more likely to be completed, while scales consisting of 30 of more items are infrequently finished. Clinicians also should consider how they plan to use the results of a PRO before implementing one; if the data will not be used, then the effort to implement and collect it will be wasted.

Barriers to PRO implementation and future directions

Given the potential benefits of PROs, why are they not implement-

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ed routinely? The integration of PROs into large health care systems languishes partly because of technological and operational barriers.[9] For instance, the manual distribution, collection, and transcription of handwritten information requires substantial investitures of time, which is magnified by the number of patients within a large health system. One approach to the technological barrier includes the creation of an electronic platform integrated with patient portals. Such a platform would obviate the need to manually collect and transcribe documents, and could import data directly into provider documentation. However, the programming time and costs are substantial upfront, and without clear data that this could lead to improved outcomes or decreased costs downstream there may be reluctance to devote resources to this. In clinical practice, the already significant demands on providers' time mitigates enthusiasm to add additional tasks. Providers also could face annual licensing agreements, fees on a per-study basis, or royalties associated with particular PROs, and at the individual practice level, there may not be appropriate expertise to select and implement routine PRO monitoring. The PROMIS project[1] tries to clarify which PROs constitute the best measure for each construct and condition.[9] The PROMIS measures also are provided publicly and are available without license or fee.

Areas well situated for growth in the use of PRO measures include comparative effectiveness studies and pragmatic clinical trials. PRO-derived data may promote a shift from explanatory randomized controlled trials to pragmatic randomized controlled trials because these data emphasize patient-centered care and are more generalizable to clinical settings. Further, the derivation of data directly from the health care delivery system through PROs, such as two-way text messages, increases the relevance and cost-effectiveness of clinical trials. Given the current medical climate, pressures continue to mount to identify cost-efficient and efficacious medical therapies.[10] PROs

Take-away points

1. There are multiple PROs that have been developed to characterize esophageal symptoms including dysphagia and heartburn, for diseases such as GERD, eosinophilic esophagitis, achalasia, and esophageal cancer.
2. Esophageal PROs can be used to monitor symptoms over time and assess treatment efficacy.
3. Implementation of esophageal PROs, both in large health systems and in routine clinical practice, is not yet standard and faces barriers such as technologic integration in the EMRs, incorporation into clinical workflows, and complexity of some PRO instruments.
4. The potent benefit of routine use of esophageal PROs include patient-centered care, more accurate and timely disease monitoring, and applicability to comparative effectiveness studies, pragmatic clinical trials, and patient-powered research networks.

Table 1. Overview of esophageal PROs for measuring dysphagia or heartburn

Condition or symptom and instrument	Target population	Longitudinal validity	Plan for scoring measure and missing data	Reference
Esophageal cancer				
FACT-E[a]	Cohort A: adults with resectable squamous or adenocarcinoma of the esophagus or gastroesophageal junction (GEJ) Cohort B: esophageal cancer patients with planned neoadjuvant chemoradiation before surgery	Yes	Yes/no	Cancer. 2006;107:854-63[13]
EORTC-QLQ-OG25	Esophageal or gastric cancer including tumors of the GEJ	No	Yes/no	Eur J Cancer. 2007;43:2066-73[14]
EORTC-QLQ-OES18	Newly diagnosed squamous cell or esophageal adenocarcinoma	No	Yes/no	Eur J Cancer. 2003;39:1384-94[15]
Cancer-attributed oropharyngeal (OP) dysphagia				
MDADI	Neoplasm of the upper aerodigestive tract	No	Yes/no	Arch Otolaryngol Head Neck Surg. 2001;127:870-6[16]
Mechanical and neuromyogenic OP dysphagia				
SWAL-QOL	Mechanical or neurologic OP dysphagia owing to multiple causes	Yes	Yes/no	Dysphagia. 2000;15:122-33[17]
SSQ	Neuromyogenic or OP dysphagia with 3 months of stable symptoms	Yes	Yes/no	Gastroenterology. 2000;118:678-87[18]
SWAL-CARE	Mechanical or neurologic OP dysphagia owing to multiple causes	No	Yes/no	Dysphagia. 2002;17:97-114[19]
Achalasia				
MADS	Achalasia patients	No	Yes/yes	Am J Gastroenterol. 2005;100:1668-76[20]
Eckardt score[a]	Newly diagnosed achalasia patients undergoing pneumatic dilatation	No	Yes/no	Gastroenterology. 1992;103:1732-38[21]
Eosinophilic esophagitis				
DSQ	Adolescents and adults with eosinophilic esophagitis (EoE)	No	Yes/yes	Aliment Pharmacol Ther. 2013;38:634-42[22]
PEESS v2.0[a]	Pediatric patients with EoE	No	No/no	BMC Gastroenterol. 2011;11:126[23]
EEsAI	Adults with EoE	No	No/no	Gastroenterology. 2014;147:1255-66.e21[24]
General dysphagia				
PROMIS-GI[a]	Multiple GI disorders and symptoms	No	Yes/no	Am J Gastroenterol. 2014;109:1804-14[1]
MDQ	Adults with dysphagia	No	No/no	Dis Esophagus. 2007;20:202-5[25]
Heartburn				
GSAS[a]	Patients with gastroesophageal reflux disease (GERD)	Yes	Yes/yes	Dig Dis Sci. 2001;46:154049[26]
N-GSSIQ	Patients with GERD confirmed with pH monitoring, endoscopy, imaging, physician diagnosis, or proton pump inhibitor response with symptoms over previous 3 months	Yes	No/yes	Aliment Pharmacol Ther. 2010;32:591-602[27]
ReQuest	Patients with GERD	Yes	No/no	Aliment Pharmacol Ther. 2004;20:891-8[28]
RDQ	GERD in primary care and clinical trials	Yes	Yes/no	Aliment Pharmacol Ther. 2007;25:1087-97[29]
PASS	Patients in clinical practice taking a proton pump inhibitor	Yes	Yes/no	Gastroenterology. 2009;136(Suppl 1):M1870[30]
GERD-Q[a]	Diagnosis of GERD in primary care	No	Yes/no	Aliment Pharmacol Ther. 2009;30:1030-8[31]

[a] Publicly available

Note: Adapted from Patel et al[5] and Vakil et al.[6]

DSQ, Dysphagia Symptom Questionnaire; EEsAI, eosinophilic esophagitis symptom activity index; EORTC QLQ-OES18, European Organization for Research and Treatment of Cancer Quality-of-Life with esophageal cancer 18 items; EORTC QLQ-OG25, European Organization for Research and Treatment of Cancer Quality-of-Life with esophageal Cancer 25 items; FACT-E, Functional Assessment of Cancer Therapy Esophageal Cancer Subscale; GSAS, GERD Symptom Assessment Scale; MADS, Measure of Achalasia Disease Severity; MDADI, M.D. Anderson dysphagia inventory; MDQ, Mayo dysphagia questionnaire; N-GSSIQ, Nocturnal Gastro-oesophageal Reflux Disease Symptom Severity and Impact Questionnaire; PASS, Proton Pump Inhibitor Acid Suppression Symptom Test; RDQ, Reflux Disease Questionnaire; SQAL-CARE, swallowing quality of care; SSQ, Sydney Swallow Questionnaire; SWAL-QOL, swallow quality-of-life questionnaire.

further consider the comparative symptom burden and side effects associated with competing treatment strategies.[11] Finally, PROs also have enabled the procurement of data from patient-powered research networks. Although this concept has not yet been applied to esophageal diseases, one example of this in the GI field is the Crohn's and Colitis Foundation of America Partners project, which has built an internet cohort consisting of approximately 14,200 inflammatory bowel disease patients who are monitored with a series of PROs.[12] An endeavor such as this should be a model for esophageal conditions in the future.

Conclusions

PROs, as a structured means of directly assessing symptoms, help facilitate a provider's understanding from a patient's perspective. Multiple PROs have been developed to characterize constructs pertinent to esophageal diseases and symptoms. These vary in methodologic rigor, but multiple well-constructed PROs exist for symptom domains such as dysphagia and heartburn, and can be used to monitor symptoms over time and assess treatment efficacy. Implementation of esophageal PROs, in both large health systems and routine clinical practice, is not yet standard and faces barriers. However, the potential benefits are substantial and include more accurate and timely disease monitoring, applicability to comparative effectiveness studies, pragmatic clinical trials, and patient-powered research networks.

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Dr. Dellon has received research funding from Adare, Allakos, Celgene/Receptos, GSK, Regeneron, Shire, and others; he has been a consultant for Adare, Allakos, Celgene/Receptos, GSK, Regeneron, Shire, and others; and has received an educational grant from Banner and Holoclara.

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Colorectal cancer: New observations, new implications

BY DAVID LIEBERMAN, MD, AGAF

The incidence and mortality of colorectal cancer (CRC) have declined by 3% per year over the past 10-15 years – a remarkable achievement. The decline in incidence has been dramatic for individuals over age 50 years, who are targeted by screening. However, the reduction in CRC risk does not apply to all populations in the United States. New epidemiologic trends and observations point to patient demographics and regional variation as potential risk factors. While such observations provide what I call "blurry snapshots," they may well have important implications for our approach to screening and prevention.


DR. LIEBERMAN

Recent evidence suggests that rates of CRC have been increasing, not decreasing, in individuals younger than age 50 years – a demographic we have traditionally regarded as low risk. This cohort accounts for more than 10% of CRC, and this trend is occurring in developed countries in Europe and Asia, as well as in the U.S.

What are the reasons? There are several personal and environmental factors that could be contributing. Obesity and metabolic syndrome are risk factors for CRC and have been more commonly developing in childhood over the past 40 years. Alteration of the microbiome could also potentially predispose one to developing CRC. The use of antibiotics in childhood was more common for some of these younger generations than it was for the preceding generations, and antibiotics have been introduced into the food industry to fatten animals. The introduction of food chemicals could also either alter the microbiome and/or promote inflammation, which could lead to neoplasia. Exposure to more ambient radiation may be another risk factor.

These hypotheses are biologically plausible – but untested. Nevertheless, this observational trend does have implications for clinicians. First, studies have shown that up to 20% of CRCs before age 50 years are associated with germline mutations, while others are associated with a family history of CRC. Therefore, it is important to capture and update family history. In addition, there is evidence that individuals aged 40-49 years with rectal bleeding have a higher risk of advanced adenomas, so our threshold for performing diagnostic colonoscopy should be lowered. African Americans also have a higher risk of CRC at a younger age than do other racial groups and might benefit from early screening at age 45 years. Notably, recent recommendations from the American Cancer Society call for consideration of screening everyone at age 45 years.

There is substantial state-to-state and county-to-county variation in the incidence and mortality of CRC. While some of this variation can be explained by racial variation, smoking, obesity, and social determinants of health, there are "hot-spots" that may defy easy explanation. There has been very little research about environmental factors (air, water, and ambient radiation). Two regions at particularly high risk are the Mississippi Delta region and Appalachia – areas where water pollution could be a factor. The substantial county-to-county variation within these high-risk areas points to a potential environmental culprit, but further research is needed.

For the GI community, there are several implications to be found in these changing demographics and risks. For one, we may need to consider expanding our risk concepts to include not only genetic and personal risk factors but also environmental factors. To mitigate risk, providers and public health officials may need to then target these high-risk areas for more intensive screening efforts.

Dr. Lieberman is a professor of medicine and chief of gastroenterology and hepatology at Oregon Health & Science University in Portland. He has no conflicts of interest.

'Game of Crohn's ... and colitis'

BY MARIA T. ABREU, MD, AGAF

Here is an update on the rapidly moving field of inflammatory bowel disease (IBD), from the power of the microbiome to the prediction of IBD and new ways to use established drugs.

We have had a high incidence and prevalence of IBD in the Western world, but since the 1990s, that rate has stabilized. Asian and Latin American countries, in the meantime, have witnessed a rapid rise in IBD. This observation offers opportunities to understand what changes in our environment or food supply may be contributing to this rise. It also has important economic implications since Asia, especially China, is highly populous; even small increases in the rates of affected patients represent huge increases in disease burden.


DR. ABREU

Regarding the microbiome, we now understand that, while the healthy microbiome is diverse and able to produce short-chain fatty acids, such as butyrate, the dysbiotic IBD microbiome is less diverse and characterized by expansion of proinflammatory pathobionts (such as *Fusobacterium*), the proliferation of sulfate-reducing bacteria, and a decrease in anti-inflammatory butyrate production.

There have now been several promising trials of fecal microbial transplant (FMT) for the treatment of ulcerative colitis (UC). The most effective strategies have involved colonic delivery of FMT, pooled donors, and repeated stool enemas to solidify the response. Following FMT, patients' microbial diversity increases. The hope is that we can use diet as a complement to maintain the diversity and generation of beneficial metabolites, as well as deliver the therapy orally.

Predicting IBD

Although we have made advances in therapy, we continue to miss opportunities to prevent long-term complications. At Digestive Disease Week,® Jean-Frederic Colombel, MD, a professor of medicine at the Icahn School of Medicine at Mount Sinai, New York, presented data on the PREDICTS study (Aliment Pharacol Ther. 2016 Jun;43[12]:1300-10), in which serum samples collected from military recruits prior to development of IBD was used to identify serologic markers that could predict those who ultimately developed Crohn's disease but not UC.

The pediatric medical community, meanwhile, has studied an inception cohort of newly diagnosed, untreated children – the RISK cohort (Lancet. 2017 Apr 29;389[10080]:1710-8) – to define some of the risk factors that predict more aggressive disease. By using biopsy tissue from the time of diagnosis, investigators could predict who would develop stricturing disease versus penetrating disease. Patients who would develop penetrating disease had up-regulation of inflammatory pathways and responded to anti–tumor necrosis factor therapy, while those who developed a stricturing phenotype had increased expression of extracellular matrix pathways and were significantly less likely to respond to anti-TNF therapy (Lancet. 2017 Apr 29;389[10080]:1710-8). These studies provide a proof of concept that we might someday be able to use for personalized approaches to treating IBD.

Using new drugs, targeting new pathways

The recently published CALM study tested the hypothesis that treating to a target of no biochemical inflammation (elevated C reactive protein or fecal calprotectin) would be better than symptom-driven treatment alone. Treatment escalation for active disease included adalimumab every other week, then weekly adalimumab, and finally the addition of azathioprine. At the end of the study, patients whose medical therapy was based on both symptoms and biochemical inflammation had a higher degree of mucosal healing than did patients in the clinical management group (Lancet. 2018 Dec 23;390[10114]:2779-89).

Ustekinumab is a monoclonal antibody that targets the p40 subunit of interleukin-12 and interleukin-23 and is approved for Crohn's

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Eosinophilic esophagitis: Facets of a new disease

BY IKUO HIRANO, MD, AGAF

A dramatic rise in the recognition of eosinophilic esophagitis (EoE) has followed the case series by Stephen Attwood, MD, and Alex Straumann, MD, which first characterized the disease 25 years ago. While still a young disease, EoE has evolved from esoterica to a leading cause of dysphagia and food impaction worldwide (Gastroenterology. 2018 Jan;154[2]:319-32.). The typical face of EoE is a 30- to 40-year-old white man, but EoE afflicts both men and women of all ages and ethnic groups.


DR. HIRANO

Guidelines prior to 2017 excluded proton pump inhibitor–responsive esophageal eosinophilia (PPIREE) from a formal diagnosis of EoE. The last decade, however, has witnessed the rise of fall of PPIREE, which was first reported in 2006 in a case series of three pediatric patients with presentations consistent with EoE, but symptom and histologic resolution after treatment with omeprazole. At the time, these cases were viewed as rare curiosities. Subsequent to a prospective series by Javier Molina-Infante, MD, in 2011, however, multiple studies have demonstrated that 30%-50% of patients suspected of having EoE respond to proton pump inhibitor (PPI). Clearly, PPIREE is not rare. Clinical and translational studies have investigated the phenomenon of PPIREE, noting that EoE and PPIREE share demographic, symptom, endoscopic, and pathologic features as well as biomarker expression and gene profiles that are distinct from gastroesophageal reflux disease (GERD). Furthermore, studies have identified intriguing, acid-independent properties of PPIs that inhibit allergic inflammation in cultured EoE cell lines. Together, these clinical and translational studies led to a 2016 European task force recommendation to remove the PPI trial from the diagnostic criteria for EoE (Gut. 2016 Mar;65[3]:524-31). At Digestive Disease Week 2017,® an international consortium sponsored by the International Gastrointestinal Eosinophil Researchers (TIGERS) convened in Chicago to review this controversy. The consensus from this meeting was in line with the European position statement. For patients with a clinical presentation suggestive of EoE and esophageal eosinophilia, clinicians should carefully consider non-EoE causes of esophageal eosinophilia but would not be required to use PPIs to establish a diagnosis of EoE.

Assessment of disease activity in EoE has largely focused on counting eosinophils on esophageal biopsies, but the mucosa may be the tip of the EoE iceberg. There is increasing evidence that the inflammation and remodeling aspects of EoE extend beneath the mucosa. If you "dig a little deeper" and sample the subepithelial space, a different face of EoE emerges, with eosinophilic inflammation and fibrosis in EoE that are distinct from GERD. This subepithelial remodeling forms the basis for the strictures and narrow caliber esophagus that are major complications of EoE.

Treatment of EoE involves a multifaceted approach that includes medications, dietary therapy, and esophageal dilation. No drugs have yet been approved by the Food and Drug Administration for EoE. Off-label use of topical corticosteroids are a mainstay of therapy, with 10 double-blind, placebo-controlled randomized trials demonstrating efficacy for

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Treatment of inflammatory bowel disease

BY DAVID S. WEINBERG, MD, MSC

The inflammatory bowel disease (IBD) session covered optimal ways to initiate treatment for ulcerative colitis and Crohn's disease, when and how to discontinue some of those treatments, and the use of biosimilars as substitutes for biologic therapies. Finally, suggestions were provided regarding the often-challenging identification of irritable bowel complaints in patients with IBD.


DR. WEINBERG

Uma Mahadevan, MD, AGAF, opened by reviewing important patient factors to consider, such as disease type and severity, comorbidities, and previous therapies, before the initiation of anti-inflammatory, immunomodulatory, and/or biologic therapies in patients with IBD. She underlined the importance of risk stratification in selecting optimal therapies as well as the role of steroid-sparing agents, and she discussed the preferability of a "treat to target" strategy that emphasizes clinical, laboratory, and endoscopic response. Finally, Dr. Mahadevan, of the University of California, San Francisco, provided an overview of the role of tofacitinib (Xeljanz), which was recently approved for the treatment of moderate to severe ulcerative colitis.

Millie D. Long, MD, MPH, discussed the clinical challenges associated with stopping biologic and/or immunomodulator therapy in selected patients with IBD. Long-term use of immunomodulators and biologics can be associated with increased risk of malignancy. Dr. Long, of the University of North Carolina, Chapel Hill, reviewed data suggesting that approximately 50% of patients will relapse within 2 years of withdrawing from either class of agents. For patients on dual therapy, similar rates are seen on withdrawal of biologics alone, although most patients can be brought back under control with drug reinitiation. In general, withdrawal is predicted to be most effective in patients who have had a durable response for at least 6-12 months with clinical, laboratory, and endoscopic evidence of remission.

Around the world, use of biosimilar anti–tumor necrosis factor agents is growing. Peter Lakatos, MD, PhD, AGAF, director of IBD Centre at McGill University, Montreal, reviewed the current literature, which demonstrates very similar clinical performance between the first generation of biosimilars and more traditional agents from this class. Food and Drug Administration approval in the United States has been slower than elsewhere. However, it is expected that multiple agents already used or under development outside this country will be available in the United States in the next several years. Biosimilars have already captured 50% of the European market and, because of cost considerations, their use is mandatory in some non-U.S. settings.

In some patients, differentiating an IBD flare from superimposed irritable bowel syndrome symptoms can be difficult. Charles Bernstein, MD, of the University of Manitoba, Winnipeg, emphasized the importance of exploring perceived stress in the life of patients with IBD. Stress can be the dominant factor driving clinical complaints in the absence of identifiable increases in inflammatory activity, he explained.

Dr. Weinberg is chairman of the department of medicine, Fox Chase Cancer Center, Philadelphia. He has no conflicts of interest.

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both histology and symptoms. Novel therapeutic approaches to EoE are targeting allergic cytokine mediators including interleukin-4, -5, and -13 with promising results. The role of biologic therapies in the management of EoE is yet undefined but the increasing recognition of steroid-refractory patients as well as potential effects on esophageal remodeling are unmet needs. Diet therapy continues to be an important, first-line option for motivated patients and clinicians, with removal of the six most common food allergens associated with a 70% histologic response in both pediatric and adult studies. Less-restrictive diets have been devised to reduce the need for repeated endoscopies. At the same time, several office-based tests of disease activity are undergoing validation, including the esophageal string test, Cytosponge, mucosal impedance, transnasal endoscopy, and confocal microscopy capsule. These technologies will lead to fewer endoscopies and may shift EoE management to the primary care or allergist's office.

Finally, it is important to acknowledge that EoE is not a "GI disease," but one that is best managed by a multifaceted approach that integrates allergists, immunologists, pathologists, radiologists, dietitians, patient advocates, and epidemiologists who are confronting this new disease. The Consortium of Eosinophilic Gastrointestinal Disease Researchers, funded by the National Institutes of Health and the Rare Diseases Clinical Research Network, is an example of a multidisciplinary collaboration that addresses fundamental questions regarding the natural history and optimal management of EoE.

Dr. Hirano is a professor of medicine, division of gastroenterology, Northwestern University, Chicago. He has received grant support from the NIH Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR, U54 AI117804). CEGIR is also supported by patient advocacy groups including the American Partnership for Eosinophilic Disorders, the CURED Foundation, and the Eosinophilic Family Coalition. Dr. Hirano has received consulting fees and research funding from Celgene, Regeneron, and Shire among others.

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disease. Various pharmaceutical companies are now developing anti-p19 antibodies, which block IL-23 only; at DDW 2018,® the anti–IL-23 mirikizumab was shown to be effective in UC. We are also seeing the availability of oral medications for IBD. Just prior to DDW, tofacitinib (N Engl J Med. 2017 May 4;376:1723-36), a Janus kinase (JAK) 1/3 inhibitor, which has an effect on multiple different cytokine pathways, received approval for UC. Other JAK inhibitors with different specificities are being tested in trials of UC and Crohn's disease.

Dr. Abreu is a professor of medicine, a professor of microbiology and immunology, and the director of the Crohn's & Colitis Center at the University of Miami Miller School of Medicine. She has no conflicts of interest.

A postgraduate tour through the biliary tree, pancreas, and liver

BY ANDREW J. MUIR, MD, MHS, FAASLD, AGAF

For the pancreatobiliary session, Michelle Ann Anderson, MD, MSc, FASGE, of the University of Michigan, Ann Arbor, reminded us about appropriate patient selection given the risk of pancreatitis after endoscopic retrograde cholangiopancreatography, also known as post-ERCP pancreatitis. Strategies to prevent post-ERCP pancreatitis include using pancreatic duct stents and using wire rather than contrast for cannulation. She recommended rectal indomethacin for all patients. Because of encouraging data, she recommended 2-3 L of lactated Ringer's solution during the procedure and recovery.

Katie Morgan, MD, from the Medical University of South Carolina, Charleston, reviewed her group's experience with 195 total pancreatectomies with islet autotransplants for chronic pancreatitis. Quality of life improved with major reductions in narcotic use, and 25% of patients were insulin free.

Bret Petersen, MD, of Mayo Clinic, Rochester, Minn., discussed multidrug-resistant infection in

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ERCP endoscopes. He reminded us of the risk of lapses in endoscope reprocessing steps and the need for monitoring. He commented on recent Food and Drug Administration's culture guidance and new technologies in development.

James Scheiman, MD, AGAF, from the University of Virginia, Charlottesville, discussed pancreatic cysts. He reviewed the controversy between the more conservative American Gastroenterological Association guidelines and the more aggressive International Consensus guidelines. He advised considering patient preferences with a multidisciplinary approach.

DR. MUIR

For the liver session, Guadalupe García-Tsao, MD, of Yale University, New Haven, Conn., discussed the controversy regarding nonselective beta-blockers. She advised caution if refractory ascites are present because of risk for renal dysfunction, but she also highlighted the benefits including reduced first and recurrent variceal hemorrhage.

Rohit Loomba, MD, from the University of California at San Diego addressed fibrosis assessments in fatty liver. In his algorithm, patients with low Nonalcoholic Fatty Liver Disease Fibrosis Score or Fibrosis-4 scores would have continued observation, while patients with medium or high scores would undergo transient elastography or magnetic resonance elastography.

Patrick Northup, MD, from the University of Virginia discussed anticoagulation for portal vein thrombosis. He also discussed consideration of transjugular intrahepatic portosystemic shunt if there are high-risk varices. Duration of anticoagulation is controversial, but this strategy may prevent decompensation and affect transplant outcomes.

Daryl Lau, MD, FRCP(C), MSc, MPH, from Harvard Medical School, Boston, reviewed the hepatitis B virus therapy controversy for e-antigen–negative patients with prolonged viral suppression. She recommended caution in general and emphasized that stage 3-4 fibrosis patients should not discontinue therapy.

The final talk was my review of hepatitis C virus treatment. I emphasized that pretreatment fibrosis assessments are critical given continued risk of hepatocellular carcinoma after cure. Challenges include identifying the remaining patients and supporting them through treatment. HCV therapies demonstrate what is possible when breakthroughs are translated to clinical care, and I was honored to participate in this course that highlighted many advances in our field.

Dr. Muir is a professor of medicine, director of gastroenterology & hepatology research at Duke Clinical Research Institute, and chief of the division of gastroenterology in the department of medicine at Duke University, all in Durham, N.C. He has received research grants from and served on the advisory boards for AbbVie, Gilead Sciences, Merck, and several other pharmaceutical companies.

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