GI & Hepatology News

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Therapeutic endoscopy expands in IBD: New clinical practice update

AGA update outlines when advanced endoscopic interventions can delay or prevent surgery and how to select patients most likely to benefit.

By Doug Brunk

Advanced therapeutic endoscopy can delay or prevent surgery in selected patients with inflammatory bowel disease (IBD), particularly those with short, low-risk strictures and endoscopically resectable colitis-associated dysplasia, according to a new AGA clinical practice update.

The update, commissioned by the AGA Institute and published in Clinical Gastroenterology and Hepatology, synthesizes recent studies and expert consensus on endoscopic management of strictures, fistulas, neoplasia, and postoperative complications in Crohn's disease (CD) and ulcerative colitis (UC).

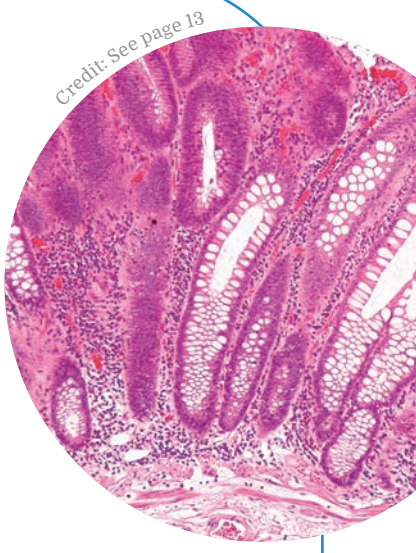
"With advances in medical therapy for IBD, fewer patients with CD or UC require surgical intervention with bowel resection," the work's senior author, Bo Shen, MD, Professor of Medicine and the Edelman-Jarislowsky Professor of Surgical Sciences at Columbia University Irving Medical Center and New York-Presbyterian Hospital, New York, told *GI & Hepatology News*. "However, prolonged disease course and medical therapy with chronic inflammation, tissue healing and remodeling often lead to structural changes (especially stricture formation), and sometimes, colitis-associated neoplasia from lead-time bias."

Continues · Page 7

Peripheral gaze guidance may improve adenoma detection rate

"Feedback on withdrawal time has also been shown to support higher ADRs [adenoma detection rates]. Despite adequate withdrawal time, substantial variability in ADR and APC persists across endoscopists, highlighting the need for additional quality metrics."

Read More • Page 13



Vonoprazan-tetracycline: A promising rescue strategy for *H. pylori*

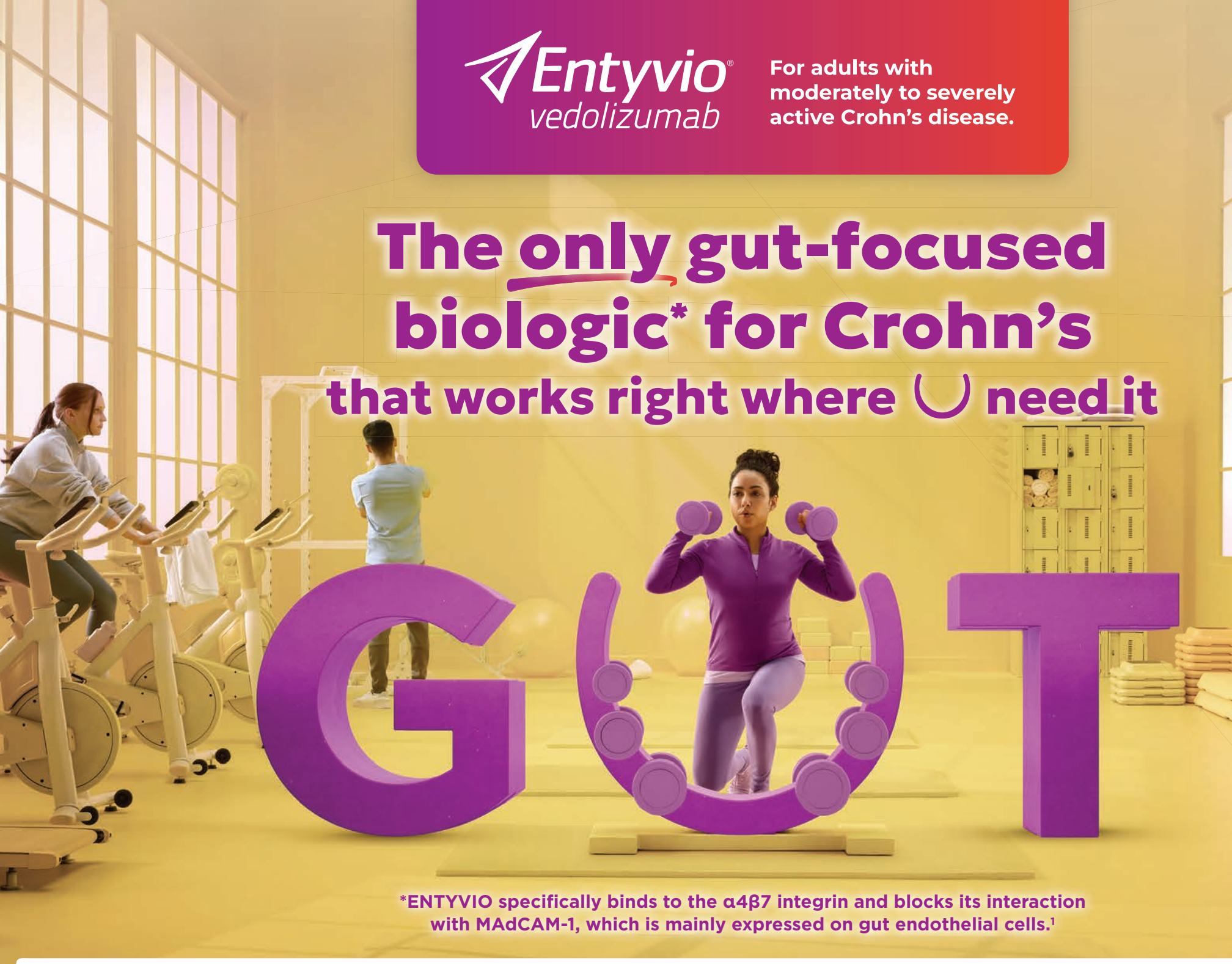
A 14-day regimen achieved eradication rates noninferior to bismuth quadruple therapy while significantly reducing adverse events in patients with prior treatment failure, according to a randomized controlled trial published in *Gastroenterology*.

Read More • Page 8

Entyvio® vedolizumab

For adults with moderately to severely active Crohn's disease.

The only gut-focused biologic* for Crohn's that works right where U need it



*ENTYVIO specifically binds to the α4β7 integrin and blocks its interaction with MAdCAM-1, which is mainly expressed on gut endothelial cells.[1]

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

ENTYVIO is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to ENTYVIO or any of its excipients.

WARNINGS AND PRECAUTIONS

- **Infusion-Related and Hypersensitivity Reactions:** Infusion-related reactions and hypersensitivity reactions including anaphylaxis, dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate have been reported. These reactions may occur with the first or subsequent infusions and may vary in their time of onset from during infusion or up to several hours post-infusion. If anaphylaxis or other serious infusion-related or hypersensitivity reactions occur, discontinue administration of ENTYVIO immediately and initiate appropriate treatment.
- **Infections:** Patients treated with ENTYVIO are at increased risk for developing infections. Serious infections have been reported in patients treated with ENTYVIO, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis, and cytomegaloviral colitis. ENTYVIO is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding ENTYVIO in patients who develop a severe infection while on treatment with ENTYVIO. Exercise caution in patients with a history of recurring severe infections. Consider screening for tuberculosis (TB) according to the local practice.
- **Progressive Multifocal Leukoencephalopathy (PML):** PML, a rare and often fatal opportunistic infection of the central nervous system (CNS), has been reported with systemic immunosuppressants, including another integrin receptor antagonist. PML typically only occurs in patients who are immunocompromised. One case of PML in an ENTYVIO-treated patient with multiple contributory factors has been reported. Although unlikely, a risk of PML cannot be ruled out. Monitor patients for any new or worsening neurological signs or symptoms that may include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. If PML is suspected, withhold dosing with ENTYVIO and refer to neurologist; if confirmed, discontinue ENTYVIO dosing permanently.
- **Liver Injury:** There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO. ENTYVIO should be discontinued in patients with jaundice or other evidence of significant liver injury.
- **Live and Oral Vaccines:** Prior to initiating treatment with ENTYVIO, all patients should be brought up to date with all immunizations according to current immunization guidelines. Patients receiving ENTYVIO may receive non-live vaccines and may receive live vaccines if the benefits outweigh the risks.

Results ◡ Need

Lasting relief and CS-free remission at Week 52[1†]

Rapid symptom relief as early as Week 6[1†]

Individual results may vary.

[†]Many patients taking ENTYVIO IV achieved remission at Week 52 vs placebo, some without steroids. Some achieved remission at Week 6. Clinical response end point was not statistically significant at Week 6. Clinical remission was defined as Crohn's CDAI score ≤150. CS-free remission is the proportion of patients receiving corticosteroids at baseline and who discontinued steroids and achieved clinical remission. Clinical response was defined as ≥100-point decrease in CDAI from baseline.

CDAI=Crohn's Disease Activity Index; CS=corticosteroid; IV=intravenous; MAdCAM-1=mucosal addressin cell adhesion molecule-1.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥3% and ≥1% higher than placebo) were: nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, pain in extremities, and injection site reactions with subcutaneous administration.

DRUG INTERACTIONS

Because of the potential for increased risk of PML and other infections, avoid the concomitant use of ENTYVIO with natalizumab products and with TNF blockers. Upon initiation or discontinuation of ENTYVIO in patients treated with CYP450 substrates, monitor drug concentrations or other therapeutic parameters, and adjust the dosage of the CYP substrate as needed.

INDICATION

Adult Crohn's Disease (CD):
ENTYVIO is indicated in adults for the treatment of moderately to severely active CD.

DOSAGE FORMS & STRENGTHS:

- ENTYVIO Intravenous Infusion: 300 mg vedolizumab; Subcutaneous Injection: 108 mg vedolizumab

Please see accompanying Brief Summary of Full Prescribing Information on adjacent pages.

Reference: 1. ENTYVIO (vedolizumab) prescribing information. Takeda Pharmaceuticals.

Explore the Results ◡ Need on ENTYVIOHCP.com

If you are a Colorado prescriber, please see the Colorado WAC disclosure form at Takeda.info/ENTYVIOCOPricing.

Takeda

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Consult the Full Prescribing Information for complete product information.

ENTYVIO (vedolizumab) for injection, for intravenous use
ENTYVIO (vedolizumab) injection, for subcutaneous use
ENTYVIO PEN (vedolizumab) injection, for subcutaneous use

INDICATIONS AND USAGE

ENTYVIO is indicated in adults for the treatment of:

- moderately to severely active ulcerative colitis (UC).
- moderately to severely active Crohn's disease (CD).

CONTRAINDICATIONS

ENTYVIO is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to ENTYVIO or any of its excipients (such as dyspnea, bronchospasm, urticaria, flushing, rash and increased heart rate) *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions and Hypersensitivity Reactions

Infusion-related reactions and hypersensitivity reactions have been reported, including anaphylaxis, dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate *[see Adverse Reactions]*. These reactions may occur with the first or subsequent infusions of ENTYVIO and may vary in their time of onset from during infusion or up to several hours post-infusion.

If anaphylaxis or other serious infusion-related or hypersensitivity reactions occur, discontinue administration of ENTYVIO immediately and initiate appropriate treatment.

Infections

Patients treated with ENTYVIO are at increased risk for developing infections *[see Adverse Reactions]*. The most commonly reported infections in clinical trials occurring at a rate greater on ENTYVIO than placebo involved the upper respiratory and nasal mucosa (e.g., nasopharyngitis, upper respiratory tract infection). Serious infections have also been reported in patients treated with ENTYVIO, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis and cytomegaloviral colitis.

ENTYVIO is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding treatment in patients who develop a severe infection while on treatment with ENTYVIO. Exercise caution when considering the use of ENTYVIO in patients with a history of recurring severe infections. Consider screening for tuberculosis (TB) according to the local practice. For progressive multifocal leukoencephalopathy (PML) *[see Warnings and Precautions]*.

Progressive Multifocal Leukoencephalopathy

PML, a rare and often fatal opportunistic infection of the central nervous system (CNS), has been reported with systemic immunosuppressants, including another integrin receptor antagonist. PML is caused by the John Cunningham (JC) virus and typically only occurs in patients who are immunocompromised. One case of PML in an ENTYVIO-treated patient with multiple contributory factors has been reported in the postmarketing setting (e.g., human immunodeficiency virus [HIV] infection with a CD4 count of 300 cells/mm^3 and prior and concomitant immunosuppression). Although unlikely, a risk of PML cannot be ruled out.

Monitor patients on ENTYVIO for any new onset, or worsening, of neurological signs and symptoms. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The progression of deficits usually leads to death or severe disability over weeks or months. If PML is suspected, withhold dosing with ENTYVIO and refer to a neurologist; if confirmed, discontinue dosing permanently.

Liver Injury

There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO. In general, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients. ENTYVIO should be discontinued in patients with jaundice or other evidence of significant liver injury *[see Adverse Reactions]*.

Live and Oral Vaccines

Prior to initiating treatment with ENTYVIO, all patients should be brought up to date with all immunizations according to current immunization guidelines. Patients receiving ENTYVIO may receive non-live vaccines (e.g., influenza vaccine injection) and may receive live vaccines if the benefits outweigh the risks. There are no data on the secondary transmission of infection by live vaccines in patients receiving ENTYVIO *[see Adverse Reactions]*.

ADVERSE REACTIONS

The following topics are also discussed in detail in the Warnings and Precautions section:

- Infusion-Related Reactions and Hypersensitivity Reactions *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*
- Progressive Multifocal Leukoencephalopathy *[see Warnings and Precautions]*
- Liver Injury *[see Warnings and Precautions]*

Clinical Trials Experience

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

The data described below reflect exposure to intravenous ENTYVIO in 3,326 patients and healthy volunteers in clinical trials, including 1,396 exposed for greater than one year, and 835 exposed for greater than two years.

Intravenous Infusion

The safety data described in *Table 2* are derived from four controlled Phase 3 trials (UC Trials I and II, and CD Trials I and III); data from adult patients receiving open-label intravenous ENTYVIO treatment at Weeks 0 and 2 (prior to entry into UC Trial II and CD Trial III) and from Weeks 6 to 52 (non-responders at Week 6 of UC Trial I and CD Trial I) are included.

In these trials, 1,434 patients received ENTYVIO 300 mg intravenously for up to 52 weeks, and 297 patients received placebo for up to 52 weeks. Of these, 769 patients had ulcerative colitis and 962 patients had Crohn's disease. Patients were exposed for a mean duration of 259 days (UC Trials I and II) and 247 days (CD Trials I and III).

Adverse reactions were reported in 52% of patients treated with intravenous ENTYVIO and 45% of patients treated with placebo (UC Trials I and II: 49% with ENTYVIO and 37% with placebo; CD Trials I and III: 55% with ENTYVIO and 47% with placebo). Serious adverse reactions were reported in 7% of patients treated with intravenous ENTYVIO compared to 4% of patients treated with placebo (UC Trials I and II: 8% with ENTYVIO and 7% with placebo; CD Trials I and III: 12% with ENTYVIO and 9% with placebo).

The most common adverse reactions (reported by ≥3% of patients treated with intravenous ENTYVIO in the UC Trials I and II and CD Trials I and III combined group and ≥1% higher than in combined placebo group) were nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain and pain in extremities *(Table 2)*.

Table 2. Adverse Reactions in ≥3% of Intravenous ENTYVIO-Treated Adult Patients and ≥1% Higher than in Placebo (UC Trials I and II* and CD Trials I and III*)

Adverse Reaction	ENTYVIO IV† (N=1434)	Placebo‡ (N=297)
Nasopharyngitis	13%	7%
Headache	12%	11%
Arthralgia	12%	10%
Nausea	9%	8%
Pyrexia	9%	7%
Upper respiratory tract infection	7%	6%
Fatigue	6%	3%
Cough	5%	3%
Bronchitis	4%	3%
Influenza	4%	2%
Back pain	4%	3%
Rash	3%	2%
Pruritus	3%	1%
Sinusitis	3%	1%
Oropharyngeal pain	3%	1%
Pain in extremities	3%	1%

* Data from patients receiving open-label intravenous ENTYVIO treatment at Weeks 0 and 2 (prior to entry into UC Trial II and CD Trial III) and from Weeks 6 to 52 (non-responders at Week 6 of UC Trial I and CD Trial I) are included.
† Patients who received ENTYVIO for up to 52 weeks.
‡ Patients who received placebo for up to 52 weeks.

Safety data for patients (n=279) in UC Trials I and II and CD Trials I and III who received intravenous ENTYVIO at Weeks 0 and 2 and were then randomized to placebo at Week 6 for up to 52 weeks, and for patients (n=416) in CD Trial II, a 10 week Crohn's disease trial, are similar to those listed in *Table 2*.

Infusion-Related Reactions and Hypersensitivity Reactions

Serious infusion-related reactions and hypersensitivity reactions including anaphylaxis have been reported following intravenous ENTYVIO administration in clinical trials *[see Warnings and Precautions]*. In UC Trials I and II and CD Trials I and III, one case of anaphylaxis [one out of 1,434 patients treated with intravenous ENTYVIO (0.07%)] was reported by a Crohn's disease patient during the second infusion (symptoms reported were dyspnea, bronchospasm, urticaria, flushing, rash and increased blood pressure and heart rate) and was managed with discontinuation of infusion and treatment with antihistamine and intravenous hydrocortisone.

In UC Trials I and II and CD Trials I and III, 4% of patients treated with intravenous ENTYVIO and 3% of patients treated with placebo experienced an infusion-related reaction (IRR). The most frequently observed IRR in the patients treated with intravenous ENTYVIO (reported more than twice) were nausea, headache, pruritus, dizziness, fatigue, infusion-related reaction, pyrexia, urticaria and vomiting (each of these adverse reactions occurred in <1% in all patients treated with intravenous ENTYVIO) and no individual adverse reaction reported occurred at a rate above 1%. These reactions generally occurred within the first two hours after the infusion and resolved with no treatment or following antihistamine and/or IV hydrocortisone treatment. Less than 1% of patients treated with intravenous ENTYVIO had IRRs assessed by the investigator as severe, and IRRs requiring discontinuation of study treatment occurred in <1%.

In clinical trials, for patients with mild IRRs or hypersensitivity reactions, physicians were allowed to pretreat with standard medical treatment (e.g., antihistamine, hydrocortisone and/or acetaminophen) prior to next infusion.

Infections

In UC Trials I and II and CD Trials I and III, the rate of infections was 0.85 per patient-year in the patients treated with intravenous ENTYVIO and 0.7 per patient-year in the patients treated with placebo *[see Warnings and Precautions]*. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, sinusitis, and urinary tract infection. Two percent of patients discontinued intravenous ENTYVIO due to infections.

In UC Trials I and II and CD Trials I and III, the rate of serious infections was 0.07 per patient-year in patients treated with intravenous ENTYVIO and 0.06 per patient-year in patients treated with placebo. Serious infections were more common in Crohn's disease patients than ulcerative colitis patients, and anal abscesses were the most frequently reported serious adverse reaction in Crohn's disease patients. Over 48 months, there was no increase in the rate of serious infections.

In controlled- and open-label long-term extension trials in adults treated with intravenous ENTYVIO, serious infections have been reported, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis and cytomegaloviral colitis.

In UC Trials I and II and CD Trials I and III, sepsis, including bacterial sepsis and septic shock, was reported in four of 1,434 (0.3%) patients treated with intravenous ENTYVIO and in two of 297 patients treated with placebo (0.7%). During these trials, two Crohn's disease patients treated with intravenous ENTYVIO died due to reported sepsis or septic shock; both patients had significant comorbidities and a complicated hospital course that contributed to the deaths. In an open-label, long-term extension trial, additional cases of sepsis (some fatal), including bacterial sepsis and septic shock, were reported. The rate of sepsis in patients with ulcerative colitis or Crohn's disease receiving intravenous ENTYVIO was two per 1,000 patient-years.

In clinical trials, all patients were screened for tuberculosis. One case of latent, pulmonary tuberculosis was diagnosed during the controlled trials with intravenous ENTYVIO. Additional cases of pulmonary tuberculosis were diagnosed during the open-label trial. All of these observed cases occurred outside the United States (U.S.), and none of the patients had extrapulmonary manifestations.

Liver Injury

There have been reports of elevations of transaminase and/or bilirubin in patients receiving intravenous ENTYVIO *[see Warnings and Precautions]*. In UC Trials I and II and CD Trials I and III, three patients reported serious adverse reactions of hepatitis, manifested as elevated transaminases with or without elevated bilirubin and symptoms consistent with hepatitis (e.g., malaise, nausea, vomiting, abdominal pain, anorexia). These adverse reactions occurred following two to five intravenous ENTYVIO doses; however, based on case report information it is unclear if the reactions indicated drug-induced or autoimmune etiology. All patients recovered following discontinuation of therapy with some requiring corticosteroid treatment. In controlled trials, the incidence of ALT and AST elevations ≥3x ULN was <2% in patients treated with intravenous ENTYVIO and in patients treated with placebo. In the open-label trial, one additional case of serious hepatitis was observed.

Malignancies

In UC Trials I and II and CD Trials I and III, malignancies (excluding dysplasia and basal cell carcinoma) were reported in six of 1,434 (0.4%) patients treated with intravenous ENTYVIO, including colon cancer (n=2), transitional cell carcinoma (n=1), breast cancer (n=1), carcinoid tumor of the appendix (n=1) and squamous cell carcinoma (n=1). Malignancy was reported in one of 297 (0.3%) patients treated with placebo (squamous cell carcinoma).

Malignancies (excluding dysplasia and basal cell carcinoma) observed during the ongoing open-label long-term extension trial included B-cell lymphoma, breast cancer, colon cancer, malignant hepatic neoplasm, malignant lung neoplasm, malignant melanoma, lung cancer of primary neuroendocrine carcinoma, renal cancer and squamous cell carcinoma. Overall, the number of malignancies in the clinical trials was small; however, long-term exposure was limited.

Subcutaneous Injection after Two Intravenous Doses of ENTYVIO

ENTYVIO was administered as a subcutaneous injection in adult patients with ulcerative colitis and Crohn's disease in double-blind, placebo-controlled clinical trials (SC UC Trial and SC CD Trial, respectively). Patients who achieved clinical response following two doses of ENTYVIO administered as an intravenous infusion at Week 0 and Week 2 were randomized 2:1 at Week 6 to ENTYVIO as a subcutaneous injection (N=106) or placebo (N=56) (SC UC Trial) and as subcutaneous injection (N=275) or placebo (N=134) (SC CD Trial).

The safety profile for up 52 weeks of total treatment was similar between patients who were switched to ENTYVIO as a subcutaneous injection in SC UC and SC CD clinical trials and patients in UC and CD clinical trials who received ENTYVIO as an intravenous infusion (*Table 2*) except for injection site reactions, which were reported with subcutaneous ENTYVIO. Injection site reactions with subcutaneous ENTYVIO were reported in 10% (11/106) of patients in SC UC Trial, including injection site erythema, rash, pruritus, swelling, bruising, and hematoma. Injection site reactions with subcutaneous ENTYVIO were reported in 3% (8/275) of patients in SC CD Trial, including injection site erythema, pruritus, urticaria, pain, rash, and edema.

Live and Oral Vaccines

There are no data on the secondary transmission of infection by live vaccines in patients receiving ENTYVIO.

In a placebo-controlled study of healthy volunteers, 61 subjects were given a single intravenous ENTYVIO 750 mg dose (2.5 times the recommended dose), and 62 subjects received placebo followed by intramuscular vaccination with Hepatitis B surface antigen and oral cholera vaccine. After intramuscular vaccination with three doses of recombinant Hepatitis B surface antigen, those treated with intravenous ENTYVIO did not have lower rates of protective immunity to Hepatitis B virus. However, those exposed to intravenous ENTYVIO did have lower seroconversion rates and anti-cholera titers relative to placebo after receiving the two doses of a killed, oral cholera vaccine. The impact on other oral vaccines and on nasal vaccines in patients is unknown.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ENTYVIO. Because these 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.

Immune system disorders: Anaphylaxis *[see Warnings and Precautions]*

Gastrointestinal system disorders: Acute Pancreatitis

Respiratory, thoracic, and mediastinal disorders: Interstitial lung disease, pneumonitis.

DRUG INTERACTIONS

Natalizumab Products

Because of the potential for increased risk of PML and other infections, avoid the concomitant use of ENTYVIO with natalizumab products.

TNF Blockers

Because of the potential for increased risk of infections, avoid the concomitant use of ENTYVIO with TNF blockers.

CYP450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of certain cytokines (e.g., IL-6, IL-10, TNFα, IFN) during chronic inflammation. Therefore, use of ENTYVIO may normalize the formation of CYP450 enzymes by modulating the underlying disease. Upon initiation or discontinuation of ENTYVIO in patients treated with CYP450 substrates, monitor drug concentrations or other therapeutic parameters, and adjust the dosage of the CYP substrate as needed. See the prescribing information of specific CYP substrates.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Available data from the Organization of Teratology Information Specialists (OTIS)/MotherToBaby ENTYVIO Pregnancy Registry, published literature and pharmacovigilance in pregnant women have not reliably identified an ENTYVIO-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes *(see Data)*. There are risks to the mother and the fetus associated with inflammatory bowel disease in pregnancy *(see Clinical Considerations)*. No fetal harm was observed in animal reproduction studies with intravenous administration of vedolizumab to rabbits and monkeys at dose levels 20 times the recommended human dosage *(see Data)*.

The background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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 miscarriage is 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and Embryo/Fetal Risk

Published data suggest that the risk of adverse pregnancy outcomes in women with inflammatory bowel disease (IBD) is associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2,500 g) infants, and small for gestational age at birth.

Fetal/Neonatal Adverse Reactions

ENTYVIO administered during pregnancy could affect immune responses in the in utero exposed newborn and infant. The clinical significance of low levels of ENTYVIO in utero-exposed infants is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown.

Data

Human Data

The vedolizumab pregnancy exposure registry conducted by OTIS/MotherToBaby study in the United States and Canada collected prospective observational data between 2015 and 2022 to assess the risk of major birth defects in live-born infants of women with ulcerative colitis (UC) or Crohn's disease (CD) treated with vedolizumab during pregnancy. The study compared pregnant patients with UC or CD exposed to vedolizumab with pregnant patients with UC or CD treated with other biological products. The registry included 99 women (58 with UC, 41 with CD) treated with vedolizumab during pregnancy, and 76 women (27 with UC, 49 with CD) exposed to other biological products during pregnancy. The proportion of major birth defects among live-born infants in patients with UC or CD treated with vedolizumab and patients with UC or CD treated with other biological products was 7.4% (7/94) and 5.6% (4/71), respectively. Overall, there was no evidence of increased risk for major structural birth defects (adjusted RR 1.07, 95% CI: 0.33, 3.52). The methodological limitations of the registry, including small sample size and the nonrandomized design, resulted in a limited ability to estimate the risk of major birth defects and other maternal and infant outcomes. The conclusions from the pregnancy registry were consistent with the published literature and pharmacovigilance.

Animal Data

A reproduction study has been performed in pregnant rabbits at single intravenous doses up to 100 mg/kg administered on gestation Day 7 (about 20 times the recommended human dosage) and has revealed no evidence of impaired fertility or harm to the fetus due to vedolizumab. A pre- and post-natal development study in monkeys showed no evidence of any adverse effect on pre- and post-natal development at intravenous doses up to 100 mg/kg (about 20 times the recommended human dosage).

Lactation

Risk Summary

Data from a clinical lactation study show the presence of vedolizumab in human milk. The mean calculated daily infant dosage was 0.02 mg/kg/day orally *(see Data)*. Systemic exposure in a breastfed infant is expected to be low because monoclonal antibodies are largely degraded in the gastrointestinal tract. There are no data on the effects of vedolizumab on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ENTYVIO and any potential adverse effects on the breastfed infant from ENTYVIO or from the underlying maternal condition.

Data

A milk-only lactation study was conducted in 9 adult lactating women being treated for active ulcerative colitis or Crohn's disease with intravenous ENTYVIO every 8 weeks after reaching steady state and completing the induction phase (ENTYVIO administration at 0, 2, and 6 weeks). Mean concentrations of ENTYVIO in human milk ranged from 0.03 to 0.26 mcg/mL. The mean calculated daily infant oral dosage was 0.02 mg/kg/day calculated as a product of the average concentration over the 8-week dosing interval and the standardized milk consumption of 150 mL/kg/day.

Pediatric Use

Safety and effectiveness of ENTYVIO in pediatric patients have not been established.

Geriatric Use

Clinical trials of ENTYVIO did not include sufficient numbers of patients aged 65 and over (72 patients with Crohn's or ulcerative colitis patients aged 65 and over were treated with ENTYVIO during controlled Phase 3 trials) to determine whether they respond differently from younger adult patients. However, no overall differences in safety or effectiveness were observed between these patients and younger adult patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Manufactured by:
Takeda Pharmaceuticals U.S.A., Inc.
Cambridge, MA 02142

U.S. License No. 1898

Revised: April 2024

For more information, go to www.ENTYVIO.com or call 1-877-TAKEDA7 (1-877-825-3327).

US-VED-3037 04/24

Shaping GI's next chapter

Robotics and precision "smart" devices are changing how we approach complex cases. Microbiome-targeted therapies offer opportunities to further personalize care.

The field of gastroenterology has a remarkable legacy of innovation. From the earliest rigid endoscopes to today's high-definition systems, each advance has sharpened our diagnostic capabilities, enhanced therapeutic precision, and improved patient safety. The advent of EMR and ESD has empowered us to treat early GI cancers less invasively, marking another leap forward.

As we look to the future, the importance of GI innovation continues to grow. Artificial intelligence now assists in polyp detection and characterization. Wireless capsule endoscopy enables noninvasive visualization of the entire GI tract. Digital health tools and remote monitoring allow proactive management of chronic diseases — even beyond the clinic walls. Robotics and precision "smart" devices are changing how we approach complex cases. Microbiome-targeted therapies offer opportunities to further personalize GI care.

This spirit of innovation comes alive at the AGA Tech Summit, which brings together innovators, entrepreneurs, industry executives, and thought leaders to explore transformative technologies shaping the future of GI care. One particularly exciting feature of this annual summit is the AGA Shark Tank — an innovation competition where creative minds pitch novel devices, diagnostics, and digital solutions to a panel of experts. Recent winners — including Twistostomy, Arithmedics, and PillBot — are already demonstrating potential to improve GI practice and patient outcomes. The 2026 Tech Summit (April 9–10 in Chicago) is an excellent opportunity to experience firsthand the excitement of the AGA Shark Tank and all that GI innovation has to offer. We hope you will consider attending.

In our April issue, we highlight the burgeoning field of endohepatology and summarize a recent AGA clinical practice update outlining expanded indications for therapeutic endoscopy in inflammatory bowel disease. From The New Gastroenterologist, Dr. Rabia De Latour (NYU) shares practical strategies to reduce the environmental impact of GI endoscopy in everyday practice. In this month's Member Spotlight, Dr. Trisha Pasricha (BIDMC) — gastroenterologist and nationally recognized medical journalist — describes how she uses humor to make complex health topics more accessible to her patients and readers.

Innovation has always defined gastroenterology — and the next chapter is just beginning.

Megan A. Adams, MD, JD, MSc
Editor in Chief

Call for nominations

Know an inspiring AGA member? Nominate them to be featured in a Member Spotlight

Do you know an AGA member with a unique, inspiring, or particularly interesting career path? Nominate them for our Member Spotlight! We would love to share their story with the AGA community. Our members are doing remarkable work in clinical care, research, education, advocacy, and innovation, and highlighting these journeys helps celebrate the diverse experiences that shape the field of gastroenterology.

To submit a nomination or suggestion, please email the member's name and a brief note about why they would be a great feature to ginews@gastro.org. We look forward to hearing about the inspiring members in your network!

GI&Hep News

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"It can be easy to identify pathology as a 'black-box': specimen goes in, diagnosis comes out."

Dr. Raul S. Gonzalez •
See Page 22

Therapeutic endoscopy expands in IBD

Continued From Page 1

While surgery can offer more definitive treatment for the structural or neoplastic complications of inflammatory bowel disease, Dr. Shen noted that it is frequently associated with postoperative anastomotic complications such as bleeding and acute or chronic leaks and recurrence of disease. "Endoscopic therapy of IBD or interventional IBD can provide more definitive therapy and less invasive treatment of structural or neoplastic complications," he said. "In addition, interventional IBD plays a growing role in the management of IBD surgery-associated complications."

Stricture management: Patient selection is key

Strictures remain common in CD. Population-based data cited in the update show that 5% to 28% of patients present with stricturing disease and more than 50% develop strictures within 10 years of diagnosis.

The authors emphasize preprocedure cross-sectional imaging to assess stricture length, prestenotic dilation, fistulas, and inflammatory activity. Endoscopic therapy is most appropriate for short strictures (<4–5 cm) in patients with fewer than three risk factors, including fistulizing disease, prestenotic dilation >5 cm, elevated C-reactive protein and prior anti–tumor necrosis factor exposure. Longer strictures (>4–5 cm), more than four strictures, or the presence of three or more risk factors generally favor surgery.

Bo Shen, MD

Binu John, MD, MPH

Endoscopic balloon dilation

Endoscopic balloon dilation (EBD) remains first-line therapy for many strictures because of its availability and favorable safety profile. Reported technical and clinical success rates range from 74% to 100%.

In a large retrospective cohort of 187 patients, technical success was 79.2%, with a 1.3% adverse event rate. A prospective, multicenter study of 95 patients reported 93.7% technical success and a 5% adverse event rate.

However, durability is limited. Cited data indicates that symptomatic recurrence occurs in about 50% of patients, and two-thirds ultimately require repeat dilation or surgery over 20 to 144 months of follow-up. The update's authors found no convincing evidence linking balloon size to perforation risk. The target dilation diameter is 18–20 mm and often requires multiple sessions. Intralesional steroid injection is not supported by current evidence.

EBD should be avoided in the presence of deep ulceration or fistula, given the risk of worsening transmural disease.

Endoscopic stricturotomy

Endoscopic stricturotomy (EST) uses electrocautery incision to dissect fibrotic tissue and is best suited for short (1–3 cm) fibrotic strictures. It may be performed alone or combined with EBD.

In a systematic review and meta-analysis of 640 EST procedures in 169 patients with CD and 118 with UC, technical success was 96.4% and clinical success 62%. Mean stricture length was 1.68 cm ± 0.84 cm. During a mean follow-up of 1.0 ± 1.1 years, 16.4% required surgery and 44.2% required additional endoscopic therapy.

According to the update, EST may be more effective than EBD and carry a lower perforation risk, but it is linked to higher delayed bleeding rates of 5%–6%. It may be particularly helpful in cases of anal canal strictures that are not easily corrected surgically.

Enteral stenting

Enteral stenting remains selective and is not routinely recommended. In a meta-analysis of nine studies including 163 patients, pooled technical success was 93% and pooled clinical success was 60.9%. Overall adverse events occurred in 15.7%, perforation in 2.7% and proximal stent migration in 6.4%. The pooled spontaneous migration rate was 43.9%.

In the randomized ProtDilat trial of 80 patients, EBD was more effective than fully covered self-expanding metal stents, with fewer repeat procedures in the EBD arm. The authors note that the stents used were designed for the esophagus and repurposed for small bowel use, limiting generalizability.

Society guidance advises against routine stenting for benign strictures. The update reserves stenting for refractory strictures in nonsurgical candidates.

Fistulas and postoperative complications

Selected short (<3 cm) ileocecal fistulas

GI & Hepatology News invited Brigid S. Boland, MD, Associate Professor of Medicine and Director of the University of California, San Diego IBD Center, to weigh in on the update.

Why is now a good time for publication of this clinical practice update (CPU)?

Dr. Boland: It has been a long time since a CPU of this kind has been published. Significant advances in endoscopic equipment have improved both our ability to detect lesions and the scope of what can be accomplished endoscopically. This is particularly true in advanced endoscopy, where the field continues to evolve rapidly. As our practices have changed, there was a clear need to update the literature to reflect current capabilities. This is also a unique area in which advanced endoscopists are frequently involved in the management of IBD patients, often prompting multidisciplinary discussions — typically between the gastroenterologist managing the IBD and the advanced endoscopist performing procedures such as a sphincterotomy.

In your opinion, what are the top two to three most important clinical scenarios discussed in the CPU?

Dr. Boland: The CPU includes very helpful alogrithms/diagrams that guide the approach to strictures, including recommendations on appropriate imaging, the role of medical therapy, the use of endoscopic balloon dilation (EBD), and indications for surgery. It also highlights key risk factors for EBD failure — such as stricture length greater than 4 cm, high BMI, proximal small-bowel strictures, prestenotic dilation, and primary strictures — which provide a useful framework for predicting the likelihood of successful dilation.

The CPU addresses colitis-associated neoplasia and provides an updated approach to dysplasia management, emphasizing that endoscopically resectable lesions should be removed endoscopically. As endoscopic resection techniques continue to evolve, the CPU supports this approach while outlining high-risk features that would favor surgical intervention.

The update also discusses the role of ESD in IBD, noting its low recurrence rates while acknowledging IBD-specific challenges such as submucosal fibrosis, which can complicate the procedure.

Finally, the CPU reviews the use of enteral stents in IBD, noting the high risk of migration — particularly given that these stents were not originally designed for the small bowel or colon. Nevertheless, it offers guidance on the narrow but defined role that stents may play in select situations.

may be amenable to endoscopic fistulotomy. In a retrospective series of 29 patients, technical success was 100%, with 3.4% adverse events.

For postoperative anastomotic leaks, the update's authors note that small acute leaks may respond to conservative management. Larger (>3 cm) abscesses can be drained percutaneously or endoscopically, with possible clip closure. Chronic sinuses may be treated with endoscopic sinusotomy or fistulotomy.

Colitis-associated neoplasia

Although the risk of colorectal cancer in IBD has declined, cumulative risk remains about 1% at 10 years, 2% at 20 years and 5% beyond 20 years.

A network meta-analysis cited in the update found dye-based chromoendoscopy detected 1.42 times more dysplastic lesions than high-definition white light endoscopy. However, the HELIOS randomized trial of 563 patients showed that high-definition white light endoscopy with segmental reinspection was noninferior to high-definition chromoendoscopy for neoplasia detection and required shorter withdrawal time.

For resection, a meta-analysis of more than 600 lesions (mean size 23 mm) removed by endoscopic mucosal resection or endoscopic submucosal dissection reported 97.9% complete resection. Local recurrence occurred in 4.9% and metachronous lesions in 7.4%, supporting continued surveillance.

The review authors noted that patients with high-risk lesions — such as those with ulceration, a nonlifting sign, or signs of invasion — should be sent for surgery. Patients with multiple lesions that cannot be removed, or dysplasia that cannot be seen, should also be referred for surgery.

Looking ahead

As therapeutic options expand, the authors anticipate broader adoption of advanced endoscopic techniques and technologies, including endoscopic ultrasound and artificial intelligence.

"We need more gastroenterologists, GI endoscopists, IBD specialists, general surgeons, and colorectal surgeons who are familiar with and feel comfortable performing therapeutic endoscopic procedures in IBD," Dr. Shen said.

Binu John, MD, MPH, Chief of Gastroenterology and Hepatology for the Miami VA Health System in Miami, Fla., cited EBD, EST, and colitis associated-neoplasia as key clinical scenarios discussed in the update. "Standard polypectomy, endoscopic mucosa resection (EMR) and endoscopic submucosal dissection (ESD) are potential endoscopic treatment options for selective lesions," said Dr. John, who was not involved in the update. "An evaluation by an advanced therapeutic endoscopist may be helpful in avoiding surgery in patients with such lesions that are amenable to endoscopic therapy."

Dr. Shen disclosed that he has served as a consultant for Janssen and has received research/education grants from AbbVie, GIE Medical, Janssen, and Takeda. Dr. John reported having no disclosures.

Vonoprazan-tetracycline: A promising rescue strategy for *H. pylori*

Two-drug regimen clears infection with fewer side effects after prior failure.

By Doug Brunk

A 14-day regimen of vonoprazan plus tetracycline achieved eradication rates noninferior to bismuth quadruple therapy while significantly reducing adverse events in patients with prior treatment failure for *Helicobacter pylori*, according to a randomized controlled trial published in *Gastroenterology*.

A team of researchers in China conducted a prospective, open-label, noninferiority trial at Peking University First Hospital in Beijing. They enrolled 350 adults with confirmed *H. pylori* infection who had failed at least one previous treatment. Participants were randomly assigned in equal numbers to receive either vonoprazan–tetracycline dual therapy (VT) or bismuth quadruple therapy (BQT) for 14 days.

The VT regimen consisted of vonoprazan 20 mg twice daily and tetracycline 500 mg three times daily. BQT included lansoprazole 30 mg twice daily, colloidal bismuth 150 mg three times daily, tetracycline 500 mg three times daily and metronidazole 400 mg three times daily. The primary outcome of interest was noninferiority in eradication rates between the two groups.

In the modified intention-to-treat analysis, eradication rates were 90.6% (154 of 170) in the VT group and 89.3% (151 of 169) in the BQT group. The between-group difference was 1.2 percentage points (P = .0003 for noninferiority), which met the prespecified criterion.

Results were consistent across analytic populations. In the intention-to-treat analysis, eradication rates were 88.0% (154 of 175) with VT and 86.3% (151 of 175) with BQT (difference, 1.7 percentage points; P = .0005 for noninferiority). In the per-protocol analysis, rates were 91.1% (153 of 168) and 92.2% (141 of 153), respectively (difference, –1.1 percentage points; P = .002 for noninferiority). No statistically significant differences in eradication were observed between groups in any population (P = .75, .84 and .88, respectively).

Subgroup analysis by penicillin allergy showed similar outcomes. In the VT group, modified intention-to-treat eradication was 91.8% (101 of 110) in patients without penicillin allergy and 88.3% (53 of 60) in those with penicillin allergy. Corresponding rates in the BQT group were 89.4% (101 of 113) and 89.3% (50 of 56). Differences did not reach statistical significance.

In other findings, approximately 70% of study participants had failed at least one prior amoxicillin-containing regimen. In the VT group, 41% had failed two or more such regimens; in the BQT group, 35% had done so.

Safety outcomes favored the dual regimen. Treatment-emergent adverse events occurred in 10.9% (19 of 175) of patients receiving VT compared with 45.7% (80 of 175) receiving BQT (P < .001). Differences were significant for mild and severe adverse events, though not for moderate events. No patients in the VT group discontinued therapy because of adverse events, compared with 8.6% (15 of 175) in the BQT group (P < .001).

Adherence, defined as taking at least 80% of prescribed doses, was higher with VT (96.0% vs 87.4%; P = .01). Eleven patients were lost to follow-up and counted as treatment failures in the intention-to-treat analysis. Among those who discontinued prematurely, 2 patients in the VT group and 16 in the BQT group took fewer than 80% of prescribed medication; 15 discontinuations in the BQT arm were attributed to adverse events.

The trial was powered assuming an 88% eradication rate for BQT as rescue therapy, requiring 166 patients per group; enrollment was increased to 175 per arm to account for anticipated dropout.

The authors noted limitations of the study, including its single-center design and the fact that VT dual therapy as a rescue regimen has not yet been evaluated outside of China.

"In this randomized controlled trial conducted in [a] Chinese population, vonoprazan–tetracycline dual therapy was shown to be an effective and well-tolerated rescue regimen for *Helicobacter pylori* infection," the authors concluded. "Its eradication rate was comparable to that of traditional tetracycline-metronidazole-based bismuth quadruple therapy, while it was associated with fewer adverse events and better adherence. By omitting bismuth and one additional antibiotic without compromising efficacy, this simplified regimen offers a practical, optimized alternative for rescue treatment, particularly for patients with penicillin allergy or with prior failure of amoxicillin-containing regimens."

The study received support from National High Level Hospital Clinical Research Funding, Natural Science Foundation of Beijing Municipality, and National High Level Hospital Clinical Research Funding.

The authors reported having no relevant disclosures.

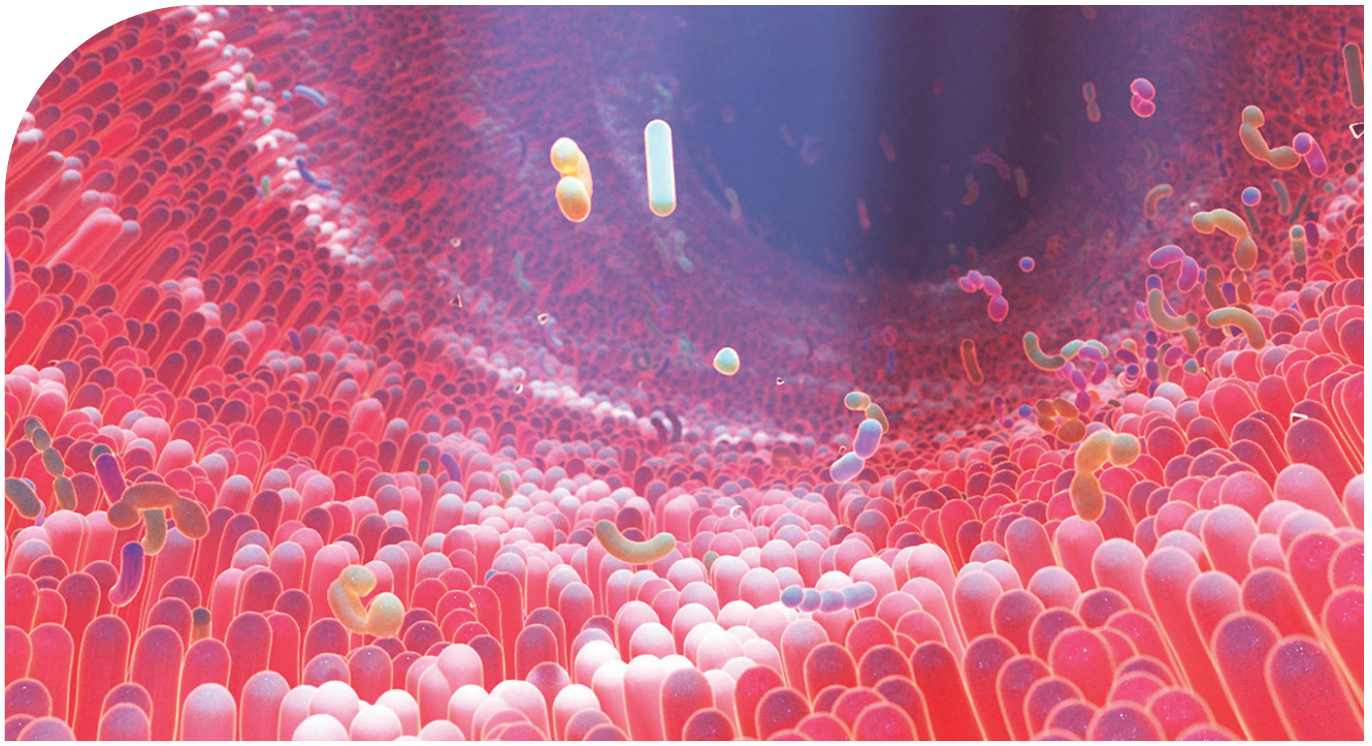
Key clinical takeaways

Vonoprazan–tetracycline dual therapy is noninferior to bismuth quadruple therapy as rescue treatment.

Dual therapy significantly improves tolerability and adherence.

Vonoprazan–tetracycline therapy may be particularly useful in patients with penicillin allergy or prior amoxicillin failure.

Credit: Adobe Stock



Diet-microbiome links drive IBD inflammation

Advanced genetic testing of gut bacteria shows certain microbes and their byproducts may help lower inflammation in Crohn's disease and ulcerative colitis.

By Doug Brunk

In a study that followed 198 adults over time, better diet quality was linked to lower inflammation in people with inflammatory bowel disease (IBD).

However, the analysis showed that the gut microbiome played different roles in Crohn's disease (CD) compared with ulcerative colitis (UC).

In the study from Spanish investigators published in *Gut*, 49 patients with CD, 49 with UC, and 100 healthy controls completed a validated 58-item food frequency questionnaire and provided stool samples at baseline and 6 months.

The researchers used shotgun metagenomic sequencing to identify which microbes were present and what functions they could perform. To assess clinical activity, they used the Harvey-Bradshaw Index (HBI) for CD and the Colitis Activity Index (CAI) for UC, and measured C-reactive protein (CRP) and fecal calprotectin in both groups of patients. Causal mediation analyses adjusted for age, sex, body mass index, smoking, infliximab, mesalazine, and recent antibiotic use.

Dietary profiles differed significantly between IBD and healthy controls at the level of food items, food groups, and macronutrients (Permutational Multivariate Analysis of Variance [PERMANOVA] q=0.0015 for all), with CD and UC clustering more tightly than healthy controls. Both IBD groups reported lower intake of vegetables, fruits, nuts/seeds, and fiber, alongside lower scores on the Alternative Mediterranean Diet (aMED), Healthy Eating Index–2015 (HEI-2015), Índice de Alimentación Saludable (IASE), the Healthy Food Diversity Index (HFD-Index), Mean Adequacy Ratio (MAR), and healthful Plant-Based Diet Index (hPDI). CD patients also had reduced carbohydrate and protein intake.

Microbial diversity followed a disease gradient: lowest in CD, intermediate in UC, highest in healthy controls (Chao1 and Shannon indices; P<.05 for pairwise comparisons). Dysbiosis scores were highest in CD. Alpha diversity correlated inversely with CRP and bowel frequency, while dysbiosis correlated positively. Higher aMED, HEI-2015, hPDI, and MAR scores were associated with greater diversity and lower dysbiosis.

The investigators found that, overall, people's usual fiber intake was not linked to levels of CRP, calprotectin, or overall disease activity. The only exception was a small link in people with Crohn's disease (CD): higher fiber intake was related to slightly lower HBI scores (Spearman ρ = −0.23; P = .049). They also found no meaningful differences in diet between people in relapse and those in remission. Changes in diet over six months were not linked to changes in inflammatory markers.

In CD, healthier dietary indices, coffee, and whole wheat bread were associated with lower HBI, but not via global diversity metrics. Instead, taxon-specific mediation was observed. Higher HEI-2015 and MAR scores and coffee intake were linked to lower HBI through increased relative abundance of *Bacteroides caccae*, Bacteroides faecis, and *Bacteroides thetaiotaomicron*, relative to *Bacteroides fragilis*. Whole wheat bread intake was mediated by increased *Butyricimonas paravirosa*, *Butyricimonas faecihominis*, and Odoribacter splanchnicus and decreased Coprobacter fastidiosus. Coffee intake was also associated with lower calprotectin via increased *Lawsonibacter asaccharolyticus* and reduced *Clostridiales bacterium*.

Functional mediation analyses showed that short-chain fatty acid (SCFA) pathways play an important role. In CD, nearly one-third of coffee's overall effect on the Harvey–Bradshaw Index (HBI) was explained by a pathway that ferments hexitols into acetate. Soft drink intake was linked to higher HBI scores, and more than 80% of this effect was explained by a mixed-acid fermentation pathway.

In UC, most of the effects were explained by overall changes in the gut microbiome. Higher unhealthy Plant-Based Diet Index (uPDI) scores were linked to higher levels of CRP and calprotectin. This was partly because these diets were associated with lower microbial diversity and more dysbiosis. Higher aMED scores were linked to lower CRP and calprotectin levels. About 60% of aMED's anti-inflammatory effect on CRP was explained by an acetate-related pathway called acetylene degradation. Fruit, coffee, and olive oil intake showed similar patterns, with their effects linked to greater microbial diversity and less dysbiosis.

The researchers acknowledged limitations of their study, including reliance on self-reported diet and treatment of repeated measures as independent observations. "In UC, diet appears to modulate inflammation primarily through restoration of microbial diversity and functional balance, whereas in CD, selective modulation of specific taxa and metabolic pathways may play a dominant role," they wrote. "These findings underscore the potential of personalized, microbiome-informed dietary strategies as complementary tools for precision management of IBD."

The study was funded by the Instituto de Salud Carlos III and co-funded by the European Union and the Spanish Ministry of Economy and Competitiveness. Additional support came from the Fondo Europeo de Desarrollo Regional and the Agency for Management of University and Research Grants.

Key clinical takeaways

Higher overall diet quality — not fiber alone — was associated with lower inflammation and improved clinical activity in IBD.

Dietary effects on inflammation were mediated differently by the microbiome in Crohn's disease (taxa- and pathway-specific) versus ulcerative colitis (overall diversity and dysbiosis).

Specific foods such as coffee, whole grains, fruits, and olive oil were linked to better outcomes via microbiome changes, while soft drinks were associated with worse disease activity.

Gastric cancer risk rises in familial adenomatous polyposis

FAP patients found to have a 12-fold higher risk of gastric cancer than the general population.

By Doug Brunk

Patients with familial adenomatous polyposis (FAP) in the Netherlands have a 12-fold higher risk of gastric cancer than the general population, and since 2020 gastric cancer has become the most frequently diagnosed malignancy in this population, according to a nationwide cohort study published in *Gastroenterology*.

Dutch investigators led by senior author Evelien Dekker, MD, PhD, of the Department of Gastroenterology and Hepatology at Amsterdam University Medical Center analyzed 1,230 patients with FAP identified through the Netherlands Foundation for Detection of Hereditary Tumors registry and the Dutch Nationwide Pathology Databank from 1975 to 2024. Median age at last follow-up was 51 years (IQR, 39-64), and 48% were women. A pathogenic APC variant was confirmed in 92.5%.

Overall, 388 patients (31.5%) developed 461 cancers. The most common were colon (n = 129), rectal (n = 77), duodenal (n = 31) and gastric (n = 28). Nearly half of colorectal cancers (49.5%) were index cancers diagnosed at initial FAP presentation.

Using Fine and Gray competing risk models, cumulative incidence at age 70 was 13.2% for colon cancer and 9.8% for rectal cancer. At age 80, estimates were 15.3% and 11.5%, respectively. Duodenal cancer incidence reached 4.4% at age 70 and 6.2% at age 80; gastric cancer incidence was 4.3% and 4.6%, respectively.

Gastric cancer cases increased from four (0.4%) in 2006-2015 to 18 (2.1%) in 2016-2024 (P < .01). Since 2020, 11 gastric cancers were diagnosed compared with four colon cancers.

Standardized incidence ratios showed significantly elevated risks for gastric cancer (SIR, 12.02), colorectal cancer (SIR, 14.22), duodenal cancer (SIR, 277.28), ampullary cancer (SIR, 113.85), small-bowel cancer (SIR, 122.03), hepatoblastoma (SIR, 747.52) and hepatocellular carcinoma (SIR, 5.43). Extraintestinal risks were also increased for thyroid (SIR, 17.35), gynecologic (SIR, 2.27) and central nervous system cancers (SIR, 3.79).

Surveillance-detected colorectal cancers were more often stage I and less often stage IV than in the general population, whereas 43% of gastric cancers were diagnosed at stage IV.

During follow-up, 262 deaths occurred vs 134 expected (SMR, 1.96). The researchers noted certain limitations of the study, including the retrospective registry design and lack of detailed surveillance data.

The authors reported having no relevant financial disclosures.

Endoscopic ultrasound pushes beyond biopsy in diagnostics

Review highlights advances that expand endoscopic ultrasound into precision diagnostics and personalized therapy across pancreatic and liver diseases.

By Doug Brunk

Credit: Adobestock.com

Endoscopic ultrasound (EUS) is moving past its traditional role as a diagnostic imaging and tissue sampling tool toward enabling early disease detection, advanced molecular profiling, and more personalized treatment strategies, according to a comprehensive review recently published in the journal *Gastroenterology*.

The review, led by Michael B. Wallace, MD, MPH, the Fred C. Andersen Professor of Medicine in the Division of Gastroenterology and Hepatology at Mayo Clinic, Jacksonville, Fla., describes how new technologies and workflows spanning molecular assays, advanced needle designs, and artificial intelligence (AI) are redefining the diagnostic potential of EUS across gastrointestinal and hepatobiliary diseases.

"In the past five years or so, there's been a great deal of appropriate attention paid to therapeutic interventions of endoscopic ultrasound, particularly because we've seen such a dramatic shift in therapeutic options with the advent of lumen-apposing metal stents, and radiofrequency ablation in particular," Dr. Wallace told *GI & Hepatology News*. "I think the advances in diagnostic endoscopic ultrasound have been underappreciated, a little bit overshadowed by those advances. So, I think that this is a very timely review."

Highlights from the article include the following:

Pancreatic and functional testing

In chronic pancreatitis (CP), EUS remains the preferred diagnostic modality when computed tomography or magnetic resonance imaging findings are inconclusive. Secretin-stimulated endoscopic pancreatic function testing (ePFT) can complement morphologic evaluation by measuring bicarbonate concentration in duodenal fluid to diagnose exocrine pancreatic insufficiency.

A prospective study cited in the review involving 145 patients with suspected early CP found diagnostic concordance between EUS and ePFT in 88 cases, allowing CP to be confidently confirmed or excluded in a large number of patients. However, discordant findings between the two modalities limited certainty. The review authors noted that added procedural time and interpretive expertise have restricted ePFT's broader adoption.

Liquid biopsy for early pancreatic cancer detection

Secretin-stimulated pancreatic juice sampling via the duodenum — performed concurrently with EUS — now enables molecular "liquid biopsy" testing without cannulation of the pancreatic duct. In one prospective cohort of 88 pancreatic cancer cases and 134 controls cited in the review, a methylated DNA marker panel *(C13orf18*, *FER1L4*, and *BMP3)* combined with serum carbohydrate antigen 19-9 achieved an area under the receiver operating characteristic curve of 0.95, surpassing CA 19-9 alone (0.91; *P* = .0135). Sensitivity and specificity were 89% and 88%, respectively.

The review's authors noted that these biomarkers, along with extracellular vesicle–derived microRNAs, are being investigated for cancer surveillance in high-risk individuals and cystic neoplasms.

Endohepatology: Pressure measurements and liver biopsy

According to the review, EUS-guided portal pressure gradient (PPG) measurement directly quantifies portal and hepatic vein pressures and strongly correlates with histologic fibrosis and clinical markers of portal hypertension. In multiple studies cited, the procedure demonstrated high technical success

Michael Wallace, MD, MPH

and low adverse event rates. AGA recently recognized EUS-PPG as a clinically available alternative to the transjugular approach.

EUS-guided liver biopsy also offers comparable yield, adequacy, and safety to percutaneous or transjugular routes, with the added advantage of sampling both hepatic lobes in the same session as PPG assessment. Dr. Wallace and his coauthors noted that elastography integrated with EUS now permits noninvasive fibrosis staging, which can potentially reduce dependence on biopsy.

Enhanced imaging: Contrast and elastography

According to the review, contrast-enhanced (CE) EUS improves visualization of microvasculature and tissue perfusion using intravenous microbubbles, distinguishing hypovascular pancreatic adenocarcinoma from hypervascular neuroendocrine tumors and inflammatory lesions. CE-EUS is especially valuable for lesions ≤2 cm and for targeting fine-needle aspiration (FNA) when gray-scale imaging is inconclusive.

Meanwhile, EUS elastography provides real-time tissue stiffness mapping to help differentiate malignant from benign pancreatic masses and lymph nodes. Combined CE-EUS and elastography improved diagnostic accuracy to more than 95% for gastrointestinal stromal tumors versus leiomyomas, according to cited evidence.

Needle designs and acquisition techniques

Advances in fine-needle biopsy (FNB) technology have driven a shift away from FNA. According to data cited in the review, third-generation "end-cutting" needles, such as Franseen and fork-tip designs, now achieve diagnostic accuracy above 90% without increasing complication risk. Meta-analyses of up to 29 randomized controlled trials found 22-gauge fork-tip and Franseen needles provided the highest diagnostic accuracy, often requiring only two passes compared with four for FNA when rapid on-site cytopathology evaluation (ROSE) is unavailable.

In the realm of aspiration procedures cited in the review, wet-suction techniques, or using saline to fill the needle, produced the best tissue quality and lower blood contamination than dry suction, whereas no-suction or slow-pull techniques were preferred for hypervascular lesions. Macroscopic on-site evaluation (MOSE) and visual on-site evaluation (VOSE) emerged as practical alternatives to ROSE, allowing real-time specimen adequacy assessment without cytopathologist assistance.

Integrating AI

According to the article, AI-based models are being developed to enhance lesion characterization, automate reporting, and aid tissue interpretation. One deep-learning model analyzing EUS images achieved 94% sensitivity and 82% specificity for distinguishing malignant from benign pancreatic lesions. Another convolutional neural network differentiated autoimmune pancreatitis from pancreatic cancer with 90% sensitivity and 93% specificity.

AI also shows promise for standardizing EUS reports. A deep learning–driven automated report system trained on more than 235,000 images achieved 91% accuracy and higher completeness versus manual documentation (91% vs 78%).

Cyst diagnostics and emerging tissue models

For pancreatic cysts, a meta-analysis cited in the review found that cyst fluid glucose levels <50 mg/dL yielded 90.8% sensitivity and 90.5% specificity for identifying mucinous cysts — performance comparable to or exceeding carcinoembryonic antigen. The combination of KRAS and GNAS mutation detection further improved molecular characterization.

Through-the-needle microforceps biopsy achieved diagnostic sensitivity and specificity of 80%, with a pooled adverse event rate of 7% across several meta-analyses. Needle-based confocal laser endomicroscopy provided 99% diagnostic accuracy for cyst typing in a recent meta-analysis, with low adverse event rates.

According to the review, EUS-acquired tissue now enables patient-derived tumor organoids, xenografts, and organotypic slice cultures that preserve the tumor microenvironment for testing individualized therapies. FNB samples have yielded successful organoid growth in 50–80% of cases, outperforming FNA specimens.

The authors reported having no relevant disclosures.

GI & Hepatology News invited Dr. Wallace to elaborate on the findings.

How might this review influence clinical practice?

Dr. Wallace: I think we're at a point now where screening for pancreatic cancer with EUS and associated imaging technologies like MRI have really come into the standard of care yet are underutilized. We now have very strong data from both the US and Europe cohorts in screening for pancreatic cancer that active screening with EUS and MRI is shifting the survival curve for pancreatic cancer through early detection. So, individuals who are at increased risk of pancreatic cancer, either because of family history or a known genetic variant, or most commonly a pancreatic cystic lesion, should undergo regular surveillance of their pancreas, EUS and MRI are the recommended technologies.

In liver disease, EUS has emerged as a true one-stop approach. It allows us to perform high-resolution endoscopic imaging, obtain liver biopsies, directly measure portal and hepatic venous pressures — often with greater accuracy than indirect measurements obtained via the internal jugular approach — and perform elastography in a single session. In addition, EUS enables both the diagnosis and treatment of varices.

Altogether, this approach allows for thorough evaluation of the impact of liver disease on the portal venous system and varices. Multiple key studies have shown that this method is highly accurate, safe, and more cost-effective compared with performing separate radiologic biopsies, pressure measurements, and endoscopic procedures.

What additional research may be needed, and what questions remain unanswered?

Dr. Wallace: I think still we have room to improve pancreatic cancer screening. Although we've made important advances, the ability to screen for solid cancers as opposed to cystic cancers is still limited because it's very difficult to detect the lesions at stage one or especially the high-grade dysplasia stage.

This review highlights a highly promising area that warrants further investigation: biomarkers, particularly pancreatic juice–based biomarkers and circulating cell-free DNA assays. Blood-based biomarkers are gaining popularity, especially as commercial tests become more widely available; however, their diagnostic accuracy remains modest.

Pancreatic juice–based biomarkers may represent an important intermediate step. For patients already undergoing upper endoscopy, pancreatic juice can be collected after secretin stimulation without the need for ERCP, making this approach relatively convenient. Additionally, improving our ability to image pancreatic cysts and reliably distinguish high-risk lesions potentially without the need for biopsy — will become important, as many patients present with small, low-risk cysts that do not require invasive sampling. Avoiding biopsy, which remains the most accurate diagnostic test but is invasive, would represent a significant advance. We are seeing rapid developments in artificial intelligence, both in EUS and in cross-sectional imaging modalities such as MRI. These innovations are likely to enable highly accurate classification of pancreatic cysts without the need for invasive tissue sampling.

Avoiding biopsy, which remains the most accurate diagnostic test but is invasive, would represent a significant advance. We are seeing rapid developments in artificial intelligence, both in EUS and in cross-sectional imaging modalities such as MRI.

Finally, once patients develop a full-blown adenocarcinoma of the pancreas, we currently really only have two options that are FDA-approved chemotherapy regimens, and it's very empiric as to what option we choose. Those two options would be combining the chemotherapy drugs gemcitabine and Abraxane or using the combination drug Folfirinox. We don't have a good way of predicting which of those two or other regimens patients will respond to, and so the ability to culture tumor cells and predict response to individual therapies, in addition to genetic factors in the tumor, I think will be an important advance.

Genetic risk tied to IBD severity

Large cohort links higher polygenic risk scores to worse outcomes, including surgery and intensive treatment.

By Doug Brunk

Marie Vibeke Vestergaard, PhD

Patients with a higher genetic risk for inflammatory bowel disease (IBD) were significantly more likely to experience a severe disease course, including major surgery, repeated hospitalizations and greater medication use, according to a nationwide Danish cohort study published in *Gastroenterology*.

The study analyzed polygenic risk scores, or PGS, for IBD susceptibility in 8,267 patients from Danish registries through September 2022 (3,732 with Crohn's disease and 4,535 with ulcerative colitis) and found a dose-response relationship between genetic risk and disease severity over time. Compared with patients in the lowest PGS quintile, those in the highest quintile had more than double the risk of major IBD-related surgery in both Crohn's disease and ulcerative colitis.

"We need tools to enable personalized medicine within IBD to improve patient outcomes," the study's corresponding author Marie Vibeke Vestergaard, PhD, of the Center for Molecular Prediction of Inflammatory Bowel Disease in the Department of Clinical Medicine, Aalborg University, Copenhagen, Denmark, told *GI & Hepatology News*. "Without this stratified approach, some patients experience prolonged uncontrolled inflammation and progressive damage while waiting for the optimal treatment for them, while others might be overtreated with expensive medicine with considerable side effects."

The investigators reported a hazard ratio of 2.74 for major surgery in Crohn's disease and 2.04 in ulcerative colitis when comparing the highest with the lowest PGS quintile. Time to prolonged IBD-related hospitalization (more than two days) was also shorter with increasing genetic risk.

Beyond discrete events, higher PGS was associated with biochemical markers of more active disease. At diagnosis, each standard-deviation increase in PGS corresponded to higher fecal calprotectin levels in both Crohn's disease (β = 0.27 log mg/kg) and ulcerative colitis (β = 0.21 log mg/kg), as well as lower hemoglobin levels in both conditions. Elevated C-reactive protein was observed with higher PGS in Crohn's disease but not in ulcerative colitis.

To capture overall disease burden, the researchers defined a composite severity outcome based on events within three years of diagnosis, including hospitalizations, surgeries and cumulative systemic corticosteroid exposure. Severe disease occurred in 31.6% of patients with Crohn's disease and 27.3% of those with ulcerative colitis. Each standard-deviation increase in PGS was associated with higher odds of severe disease in both groups. In absolute terms, 39.2% of Crohn's disease patients in the highest PGS quintile developed severe disease, compared with 23.6% in the lowest quintile.

Among patients diagnosed since 2003, higher PGS was linked to increased use of biologic therapies, immunomodulators and systemic corticosteroids within three years of diagnosis. For example, the odds of receiving biologic therapy rose by 35% per standard-deviation increase in PGS in Crohn's disease and by 31% in ulcerative colitis.

Subgroup and sensitivity analyses revealed differences between the two diseases. In Crohn's disease, much of the association between PGS and disease severity was attenuated after adjusting for disease location, suggesting that where the disease is located helps explain this relationship. In ulcerative colitis, the results changed very little after adjusting for disease extent, indicating that the same genetic factors influence both disease risk and severity.

Dr. Vestergaard described the positive association as "surprising and provides new insights to the etiology of disease severity linking increased susceptibility to increased severity," she said. "But what was most surprising was that the association appeared to be mediated by the location of the disease in CD. Thus, genetics influence where in the gastrointestinal tract you will get inflammation and then the location influences the disease severity."

The authors noted several limitations, including restriction to patients of European ancestry, incomplete data for some and potential selection bias in analyses relying on pathology records.

Dr. Vestergaard had no disclosures to report.

GI & Hepatology News invited Greg Gibson, PhD, professor of biology and director of the Center for Integrative Genomics at Georgia Tech, to comment on the study.

Why is this study important?

Dr. Gibson: First, it overturns the accepted almost a decade-old opinion that PGS for IBD susceptibility do not associate with disease course or severity. This study shows clearly that they do in the Danish setting. Second, it refocuses our attention on prediction of disease course, which has much more potential utility than attempting to predict disease onset.

What are the potential clinical implications of the research?

Dr. Gibson: I think it is underappreciated that precision (positive predictive value) of IBD is never going to be useful for a rare disease like IBD just because the case-control ratio is so small in the population. By contrast, if 30% of the patients advance to severe disease, as is the case in these two typical studies, then PPV can be 75% for a good predictor. We're certainly not there yet, the authors acknowledge that, but they have a line in the discussion that I think is great.

What additional research may be needed/what questions remain unanswered?

Dr. Gibson: First, this study uses the susceptibility PGS, and if it works reasonably well, then there is every likelihood that a better PGS developed to predict progression will do even better. So, this study motivates genome-wide association studies on progression. Similarly, is it possible to refine predictors independently for UC and CD? Other questions include how best to integrate PGS with biochemical, histological, radiological, pharmaceutical, and other data types. The molecular basis underlying the association between PGS and disease progression also remains unanswered. In CD it seems to relate to extent of disease, but that is not the case for UC.

From a clinical perspective, though, what is needed now is prospective research on whether or not patients wish to know their estimated risk of progression based on the PGS. Does someone in the lowest decile find some comfort in knowing that their likelihood of progressing to colectomy is only 15%, or conversely, do patients in the top decile become depressed learning their prognosis is poor? Or does this help physicians prepare for a high likelihood of progression? Or relatedly, does inclusion of this information alter the modality of treatment (specifically, early use of biologics), and does that improve outcomes while containing costs? For this, a randomized clinical trial is needed.

Is there anything else you'd like to say about this work?

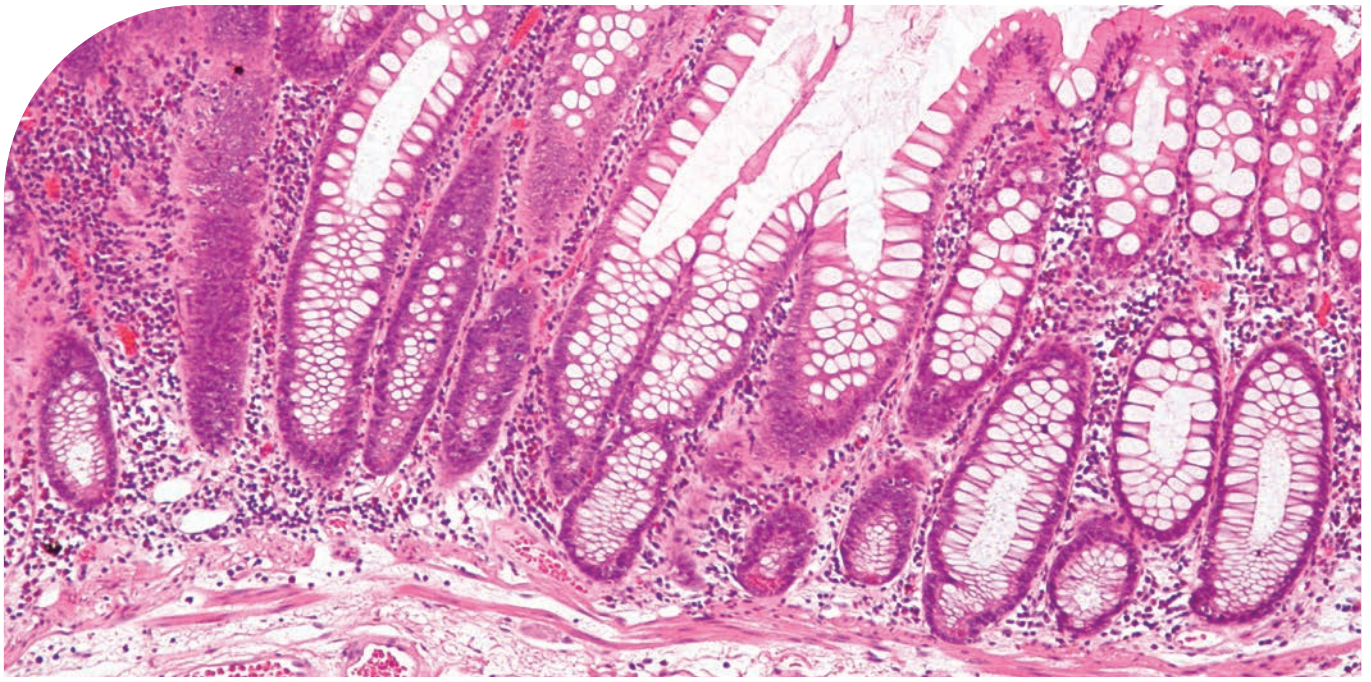
Dr. Gibson: All that genetics can do is improve the odds or bias the patient to the most appropriate therapeutic option(s). That is no different from standard medical practice, but this information is potentially powerful. The authors are not saying that you can predict disease course; they are saying that some people are more likely to progress to severe disease than others and we can see that at diagnosis. If this knowledge improves the outcome for even a quarter of patients, or prevents unnecessary biologic usage and contains costs for example, then it is a win for medical care in general, without being a precise answer for any individual patient.

Dr. Gibson reported having no relevant disclosures.

Peripheral gaze guidance may improve adenoma detection rate

The technique "significantly improved adenoma detection — particularly for flat lesions — regardless of endoscopist experience level."

By Doug Brunk



Credit: Nephron - Own work, CC BY-SA 3.0

Real-time guidance that prompts endoscopists to look toward the periphery of the colonoscopy screen significantly increased adenoma detection rate (ADR) compared with standard practice, without lengthening withdrawal time, according to a multicenter randomized controlled trial conducted in Japan.

"Ensuring adequate withdrawal time is an important surrogate marker for improving ADR and APC [adenomas per colonoscopy]," noted corresponding author Satoshi Ono, PhD, of the department of gastroenterology and gastrointestinal endoscopy at Tokyo Metropolitan Institute for Geriatrics and Gerongology, and colleagues. "Feedback on withdrawal time has also been shown to support higher ADRs. Despite adequate withdrawal time, substantial variability in ADR and APC persists across endoscopists, highlighting the need for additional quality metrics."

In the EYE-SIGHT trial, 400 patients aged 40 to 90 years undergoing colonoscopy at four institutions were randomized to eye-tracking and feedback (ETF)–guided withdrawal or usual colonoscopy. The primary endpoint, APC, was higher in the intervention group than in controls (1.34 vs 0.95), according to the research published in *Clinical Gastroenterology and Hepatology*.

ADR also improved, rising to 53.3% with gaze guidance compared with 39.2% in the control group. Polyp detection rate was 66.5% vs 47.2%. Observation time did not differ significantly between groups (8.4 vs 8 minutes). Advanced adenoma and sessile serrated lesion detection rates were similar.

The researchers used a web-based system to stratify patients by age, sex and institution. Patients were blinded to allocation; endoscopists were not. Eighteen endoscopists, including experts and non-experts, performed procedures.

"Despite adequate withdrawal time, substantial variability in ADR and APC persists across endoscopists."

Baseline characteristics, including age, sex distribution, bowel preparation quality and sedation use, were balanced between groups.

The ETF system used a screen-mounted eye tracker that recorded gaze coordinates in real time. The endoscopy monitor was divided into a 5×5 screen grid, and the 16 outer segments were designated as the areas of interest. During withdrawal in the intervention group, a high-pitched tone sounded when gaze fell within peripheral segments and a low-pitched warning tone when it did not. Controls received a continuous tone without gaze-dependent feedback.

Lesion-level analyses showed that the intervention increased detection of 5- to 9-mm adenomas, flat-type adenomas and left-sided adenomas. In per-protocol analyses, right-sided detection was also higher. Detection of lesions 10 mm or more did not differ between groups.

Gaze analysis in 340 patients confirmed that peripheral gaze rate was significantly higher in the intervention arm (33.7% vs 25.8%). In multivariable analysis, a peripheral gaze rate above 26% independently predicted adenoma detection (odds ratio 2.07), along with older age and male sex.

The benefit was concentrated among endoscopists with lower baseline peripheral gaze rates. Those starting below 26% showed significant gains in both gaze rate and ADR, while those already at or above that threshold did not improve.

The authors noted limitations of the analysis, including use of a proprietary ETF system, lack of improvement in advanced adenoma detection, absence of endoscopist blinding, and enrollment of endoscopists with baseline ADRs of at least 25%, which limits generalizability to low detectors.

"Peripheral gaze guidance significantly improved adenoma detection — particularly for flat lesions — regardless of endoscopist experience level," the authors reported. "Importantly, this intervention did not increase procedure time, suggesting no additional procedural burden. However, no improvement in AADR [advanced adenoma detection rate] or SSLDR [sessile serrated lesion detection rate] was observed. A subsequent large-scale trial involving endoscopists across diverse settings, particularly low-detector endoscopists, is needed to evaluate user ergonomics and validate improvements in clinically relevant metric."

The work was supported by Japanese Society for the Promotion of Science and the Kowa Life Science Foundation. Two of the 12 study authors reported receiving honoraria for lectures from Fujifilm Corporation and Olympus Corporation. The other authors declared no conflicts of interest.

Key clinical takeaways

Peripheral gaze guidance increased ADR compared with standard colonoscopy (53.3% vs 39.2%).

APC rates were significantly higher with gaze guidance (1.34 vs 0.95).

Flat lesions and 5–9 mm adenomas were detected more frequently in the intervention group.

Withdrawal time did not increase, suggesting the system does not add procedural burden.

Endoscopists with lower baseline peripheral gaze rates benefited most, indicating a potential role for targeted training tools.

Advanced adenoma and sessile serrated lesion detection rates did not improve, highlighting an area for further study.

HELP PATIENTS GET THE RELIEF THEY DESERVE

INDICATIONS[1]

RINVOQ is indicated for the treatment of adults with:

- **Moderately to severely active Crohn's disease (CD)** who have had an inadequate response or intolerance to one or more tumor necrosis factor (TNF) blockers. If TNF blockers are clinically inadvisable, patients should have received at least one approved systemic therapy prior to use of RINVOQ.
- **Moderately to severely active ulcerative colitis (UC)** who have had an inadequate response or intolerance to one or more TNF blockers. If TNF blockers are clinically inadvisable, patients should have received at least one approved systemic therapy prior to use of RINVOQ.

Limitations of Use: RINVOQ is not recommended for use in combination with other Janus kinase (JAK) inhibitors, biological therapies for CD or UC, or with potent immunosuppressants such as azathioprine and cyclosporine.

Please see additional Important Safety Information for RINVOQ, including BOXED WARNING on Serious Infections, Mortality, Malignancies, Major Adverse Cardiovascular Events, and Thrombosis, on the following pages of this advertisement.

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

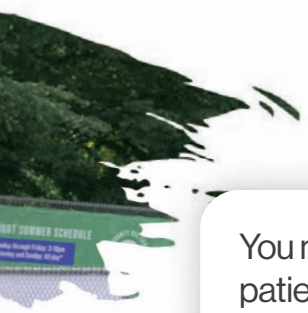
For adults with moderate to severe Crohn's disease (CD) or ulcerative colitis (UC) after inadequate response to a TNFi or another approved systemic therapy if a TNFi is clinically inadvisable[1]

NEW *EXPANDED* INDICATIONS in Crohn's and UC[1]

RINVOQ®
upadacitinib

ALSO AVAILABLE AFTER ANY BIOLOGIC OR ANOTHER APPROVED SYSTEMIC THERAPY

if a TNFi is clinically inadvisable



You may already be familiar with RINVOQ as a treatment option when treating your adult Crohn's and UC patients who have had an inadequate response or intolerance to a TNFi. Now, RINVOQ can also be used after any first-line biologic or another approved systemic therapy if a TNFi is clinically inadvisable.

Ultimately, the determination of what is *clinically inadvisable* rests with the treating healthcare professionals, based on their medical judgment and the individual needs of each patient.

DO YOU HAVE PATIENTS WHO MAY BE RINVOQ READY?

VISIT RINVOQHCP.COM/GASTROENTEROLOGY TO LEARN MORE

TNFi=tumor necrosis factor inhibitor.

SAFETY CONSIDERATIONS[1]

Serious Infections: RINVOQ-treated patients are at increased risk of serious bacterial (including tuberculosis [TB]), fungal, viral, and opportunistic infections leading to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants, such as methotrexate or corticosteroids.

Mortality: A higher rate of all-cause mortality, including sudden cardiovascular (CV) death, was observed with a Janus kinase inhibitor (JAKi) in a study comparing another JAKi with tumor necrosis factor (TNF) blockers in rheumatoid arthritis (RA) patients ≥50 years with ≥1 CV risk factor.

Malignancies: Malignancies have occurred in RINVOQ-treated patients. A higher rate of lymphomas and lung cancer (in current or past smokers) was observed with another JAKi when compared with TNF blockers in RA patients.

Major Adverse Cardiovascular Events: A higher rate of CV death, myocardial infarction, and stroke was observed with a JAKi in a study comparing another JAKi with TNF blockers in RA patients ≥50 years with ≥1 CV risk factor. History of smoking increases risk.

Thromboses: Deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients treated for inflammatory conditions with JAK inhibitors, including RINVOQ. A higher rate of thrombosis was observed with another JAKi when compared with TNF blockers in RA patients.

Hypersensitivity: RINVOQ is contraindicated in patients with hypersensitivity to RINVOQ or its excipients.

Other Serious Adverse Reactions: Hypersensitivity Reactions, Gastrointestinal Perforations, Laboratory Abnormalities, and Embryo-Fetal Toxicity.

IMPORTANT SAFETY INFORMATION[1]

SERIOUS INFECTIONS

Patients treated with RINVOQ 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 RINVOQ until the infection is controlled.

Reported infections include:

- **Active tuberculosis (TB), which may present with pulmonary or extrapulmonary disease. Test patients for latent TB before RINVOQ use and during therapy. Consider treatment for latent TB infection prior to RINVOQ use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

Carefully consider the risks and benefits of treatment with RINVOQ prior to initiating therapy in patients with chronic or recurrent infection. Monitor patients closely for the development of signs and symptoms of infection during and after treatment with RINVOQ, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

MORTALITY

In a large, randomized, postmarketing safety study comparing another Janus kinase (JAK) inhibitor with tumor necrosis factor (TNF) blockers in rheumatoid arthritis (RA) patients ≥50 years old with at least one cardiovascular (CV) risk factor, a higher rate of all-cause mortality, including sudden CV death, was observed with the JAK inhibitor. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ.

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with RINVOQ.

In a large, randomized, postmarketing safety study comparing another JAK inhibitor with TNF blockers in RA patients, a higher rate of malignancies (excluding non-melanoma skin cancer [NMSC]), lymphomas, and lung cancer (in current or past smokers) was observed with the JAK inhibitor. Patients who are current or past smokers are at additional increased risk.

With RINVOQ, consider the benefits and risks for the individual patient prior to initiating or continuing therapy, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy when on treatment, and patients who are current or past smokers. NMSCs have been reported in patients treated with RINVOQ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer. Advise patients to limit sunlight exposure by wearing protective clothing and using sunscreen.

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

In a large, randomized, postmarketing study comparing another JAK inhibitor with TNF blockers in RA patients ≥50 years old with at least one CV risk factor, a higher rate of MACE (defined as cardiovascular death, myocardial infarction, and stroke) was observed with the JAK inhibitor. Patients who are current or past smokers are at additional increased risk. Discontinue RINVOQ in patients that have experienced a myocardial infarction or stroke.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ, particularly in patients who are current or past smokers and patients with other CV risk factors. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

THROMBOSIS

Thromboses, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated for inflammatory conditions with JAK inhibitors, including RINVOQ. Many of these adverse events were serious and some resulted in death. In a large, randomized, postmarketing study comparing another JAK inhibitor to TNF blockers in RA patients ≥50 years old with at least one CV risk factor, a higher rate of thrombosis was observed with the JAK inhibitor. Avoid RINVOQ in patients at risk. Patients with symptoms of thrombosis should discontinue RINVOQ and be promptly evaluated.

HYPERSENSITIVITY

RINVOQ is **contraindicated** in patients with known hypersensitivity to upadacitinib or any of its excipients. Serious hypersensitivity reactions, such as anaphylaxis and angioedema, were reported in patients receiving RINVOQ in clinical trials. If a clinically significant hypersensitivity reaction occurs, discontinue RINVOQ and institute appropriate therapy.

GASTROINTESTINAL PERFORATIONS

Gastrointestinal (GI) perforations have been reported in clinical trials with RINVOQ. Monitor RINVOQ-treated patients who may be at risk for GI perforation (e.g., patients with a history of diverticulitis and patients taking NSAIDs or corticosteroids). Promptly evaluate patients presenting with new onset abdominal pain for early identification of GI perforation.

LABORATORY ABNORMALITIES

Neutropenia

Treatment with RINVOQ was associated with an increased incidence of neutropenia (absolute neutrophil count [ANC] <1000 cells/mm^3). Treatment with RINVOQ is not recommended in patients with an ANC <1000 cells/mm^3. Evaluate neutrophil counts at baseline and thereafter according to routine patient management.

Lymphopenia

Absolute lymphocyte counts (ALC) <500 cells/mm^3 were reported in RINVOQ-treated patients. Treatment with RINVOQ is not recommended in patients with an ALC <500 cells/mm^3. Evaluate at baseline and thereafter according to routine patient management.

Anemia

Decreases in hemoglobin levels to <8 g/dL were reported in RINVOQ-treated patients. Treatment should not be initiated or should be interrupted in patients with hemoglobin levels <8 g/dL. Evaluate at baseline and thereafter according to routine patient management.

Lipids

Treatment with RINVOQ was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Manage patients according to clinical guidelines for the management of hyperlipidemia. Evaluate patients 12 weeks after initiation of treatment and thereafter according to the clinical guidelines for hyperlipidemia.

Liver enzyme elevations

Treatment with RINVOQ was associated with increased incidence of liver enzyme elevation compared to placebo. Evaluate at baseline and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury. If increases in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) are observed during routine patient management and drug-induced liver injury is suspected, RINVOQ should be interrupted until this diagnosis is excluded.

EMBRYO-FETAL TOXICITY

Based on findings in animal studies, RINVOQ may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with RINVOQ and for 4 weeks after the final dose. Verify pregnancy status of females of reproductive potential prior to starting treatment with RINVOQ.

VACCINATION

Avoid use of live vaccines during, or immediately prior to, RINVOQ therapy. Prior to initiating RINVOQ, patients should be brought up to date on all immunizations, including prophylactic varicella zoster or herpes zoster vaccinations, in agreement with current immunization guidelines.

MEDICATION RESIDUE IN STOOL

Reports of medication residue in stool or ostomy output have occurred in patients taking RINVOQ. Most reports described anatomic or functional GI conditions with shortened GI transit times. Instruct patients to contact their healthcare provider if medication residue is observed repeatedly. Monitor patients clinically and consider alternative treatment if there is an inadequate therapeutic response.

LACTATION

There are no data on the presence of RINVOQ in human milk, the effects on the breastfed infant, or the effects on milk production. Available data in animals have shown the excretion of RINVOQ in milk. Advise patients that breastfeeding is not recommended during treatment with RINVOQ and for 6 days after the last dose.

HEPATIC IMPAIRMENT

RINVOQ is not recommended for use in patients with severe hepatic impairment.

ADVERSE REACTIONS

The most common adverse reactions in RINVOQ clinical trials were upper respiratory tract infections, herpes zoster, herpes simplex, bronchitis, nausea, cough, pyrexia, acne, headache, peripheral edema, increased blood creatine phosphokinase, hypersensitivity, folliculitis, abdominal pain, increased weight, influenza, fatigue, neutropenia, myalgia, influenza-like illness, elevated liver enzymes, rash, and anemia.

Inform patients that retinal detachment has been reported in clinical trials with RINVOQ. Advise patients to immediately inform their healthcare provider if they develop any sudden changes in vision while receiving RINVOQ.

Dosage Forms and Strengths: RINVOQ is available in 15 mg, 30 mg, and 45 mg extended-release tablets.

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

Reference: 1. RINVOQ [package insert]. North Chicago, IL: AbbVie Inc.

abbvie

RINVOQ®
upadacitinib

RINVOQ® (RIN-VOKE) (upadacitinib) extended-release tablets, for oral use
RINVOQ® LQ (RIN-VOKE) (upadacitinib) oral solution

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS, and THROMBOSIS

SERIOUS INFECTIONS

Patients treated with RINVOQ/RINVOQ LQ are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions, Adverse Reactions]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt RINVOQ/RINVOQ LQ 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 RINVOQ/RINVOQ LQ use and during therapy. Treatment for latent infection should be considered prior to RINVOQ/RINVOQ LQ use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with RINVOQ/RINVOQ LQ 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 RINVOQ/RINVOQ LQ, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy *[see Warnings and Precautions]*.

MORTALITY

In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing another Janus kinase (JAK) inhibitor to tumor necrosis factor (TNF) blockers, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with the JAK inhibitor *[see Warnings and Precautions]*.

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with RINVOQ. In RA patients treated with another JAK inhibitor, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk *[see Warnings and Precautions]*.

MAJOR ADVERSE CARDIOVASCULAR EVENTS

In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue RINVOQ/RINVOQ LQ in patients that have experienced a myocardial infarction or stroke *[see Warnings and Precautions]*.

THROMBOSIS

Thromboses, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated for inflammatory conditions with JAK inhibitors, including RINVOQ. Many of these adverse events were serious and some resulted in death. In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid RINVOQ/RINVOQ LQ in patients at risk. Patients with symptoms of thrombosis should discontinue RINVOQ/RINVOQ LQ and be promptly evaluated *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Rheumatoid Arthritis

RINVOQ® is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more TNF blockers.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biologic disease-modifying antirheumatic drugs (DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine.

Ulcerative Colitis

RINVOQ is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response or intolerance to one or more TNF blockers. If TNF blockers are clinically inadvisable, patients should have received at least one approved systemic therapy prior to use of RINVOQ.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biological therapies for UC, or with potent immunosuppressants such as azathioprine and cyclosporine.

Crohn's Disease

RINVOQ is indicated for the treatment of adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response or intolerance to one or more TNF blockers. If TNF blockers are clinically inadvisable, patients should have received at least one approved systemic therapy prior to use of RINVOQ.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biological therapies for CD, or with potent immunosuppressants such as azathioprine and cyclosporine.

CONTRAINDICATIONS

RINVOQ/RINVOQ LQ is contraindicated in patients with known hypersensitivity to upadacitinib or any of its excipients *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Serious Infections

Serious and sometimes fatal infections have been reported in patients receiving RINVOQ. The most frequent serious infections reported with RINVOQ included pneumonia and cellulitis *[see Adverse Reactions]*. Among opportunistic infections, tuberculosis, multidermatomal herpes zoster, oral/esophageal candidiasis, and cryptococcosis, were reported with RINVOQ. A higher rate of serious infections was observed with RINVOQ 30 mg compared to RINVOQ 15 mg.

Avoid use of RINVOQ/RINVOQ LQ in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating RINVOQ/RINVOQ LQ 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.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with RINVOQ/RINVOQ LQ. Interrupt RINVOQ/RINVOQ LQ if a patient develops a serious or opportunistic infection.

A patient who develops a new infection during treatment with RINVOQ/RINVOQ LQ should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and RINVOQ/RINVOQ LQ should be interrupted if the patient is not responding to antimicrobial therapy. RINVOQ/RINVOQ LQ may be resumed once the infection is controlled.

Tuberculosis

Evaluate and test patients for latent and active tuberculosis (TB) infection prior to administration of RINVOQ/RINVOQ LQ. Patients with latent TB should be treated with standard antimycobacterial therapy before initiating RINVOQ/RINVOQ LQ. RINVOQ/RINVOQ LQ should not be given to patients with active TB. Consider anti-TB therapy prior to initiation of RINVOQ/RINVOQ LQ in patients with previously untreated latent TB or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB but who have risk factors for TB infection.

Consultation with a physician with expertise in the treatment of TB is recommended to aid in the decision about whether initiating anti-TB therapy is appropriate for an individual patient.

During RINVOQ/RINVOQ LQ use, monitor patients for the development of signs and symptoms of TB, including patients who tested negative for latent TB infection prior to initiating therapy.

Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster) and hepatitis B virus reactivation, were reported in clinical trials with RINVOQ *[see Adverse Reactions]*. The risk of herpes zoster appears to be higher in patients treated with RINVOQ in Japan. If a patient develops herpes zoster, consider temporarily interrupting RINVOQ/RINVOQ LQ until the episode resolves.

Screening for viral hepatitis and monitoring for reactivation should be performed in accordance with clinical guidelines before starting and during therapy with RINVOQ/RINVOQ LQ. Patients who were positive for hepatitis C antibody and hepatitis C virus RNA, were excluded from clinical trials. Patients who were positive for hepatitis B surface antigen or hepatitis B virus DNA were excluded from clinical trials. However, cases of hepatitis B reactivation were still reported in patients enrolled in the Phase 3 trials of RINVOQ. If hepatitis B virus DNA is detected while receiving RINVOQ/RINVOQ LQ, a liver specialist should be consulted.

Mortality

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed in patients treated with the JAK inhibitor compared with TNF blockers.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ/RINVOQ LQ.

Malignancy and Lymphoproliferative Disorders

Malignancies, including lymphomas, were observed in clinical trials of RINVOQ *[see Adverse Reactions]*.

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients, a higher rate of malignancies (excluding NMSC) was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lymphomas was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lung cancers was observed in current or past smokers treated with the JAK inhibitor compared to those treated with TNF blockers. In this study, current or past smokers had an additional increased risk of overall malignancies.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ/RINVOQ LQ, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy when on treatment, and patients who are current or past smokers.

Non-Melanoma Skin Cancer

NMSCs have been reported in patients treated with RINVOQ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Exposure to sunlight and UV light should be limited by wearing protective clothing and using a broad-spectrum sunscreen.

Major Adverse Cardiovascular Events

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke was observed with the JAK inhibitor compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ/RINVOQ LQ, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. Discontinue RINVOQ/RINVOQ LQ in patients that have experienced a myocardial infarction or stroke.

Thrombosis

Thromboses, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis, have occurred in patients treated for inflammatory conditions with JAK inhibitors, including RINVOQ. Many of these adverse events were serious and some resulted in death *[see Adverse Reactions]*.

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, higher rates of overall thrombosis, DVT, and PE were observed compared to those treated with TNF blockers.

If symptoms of thrombosis occur, patients should discontinue RINVOQ/RINVOQ LQ and be evaluated promptly and treated appropriately. Avoid RINVOQ/RINVOQ LQ in patients that may be at increased risk of thrombosis.

Hypersensitivity Reactions

Serious hypersensitivity reactions such as anaphylaxis and angioedema were reported in patients receiving RINVOQ in clinical trials. If a clinically significant hypersensitivity reaction occurs, discontinue RINVOQ/RINVOQ LQ and institute appropriate therapy *[see Adverse Reactions]*.

Gastrointestinal Perforations

Gastrointestinal perforations have been reported in clinical trials with RINVOQ *[see Adverse Reactions]*.

Monitor RINVOQ/RINVOQ LQ-treated patients who may be at risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis and those taking concomitant medications including NSAIDs or corticosteroids). Evaluate promptly patients presenting with new onset abdominal pain for early identification of gastrointestinal perforation.

Laboratory Abnormalities

Neutropenia

Treatment with RINVOQ was associated with an increased incidence of neutropenia (ANC less than 1000 cells/mm^3).

Evaluate neutrophil counts at baseline and thereafter according to routine patient management. Avoid RINVOQ/RINVOQ LQ initiation and interrupt RINVOQ/RINVOQ LQ treatment in patients with a low neutrophil count (i.e., ANC less than 1000 cells/mm^3).

Lymphopenia

ALC less than 500 cells/mm^3 were reported in RINVOQ-treated patients in clinical trials.

Evaluate lymphocyte counts at baseline and thereafter according to routine patient management. Avoid RINVOQ/RINVOQ LQ initiation or interrupt RINVOQ/RINVOQ LQ treatment in patients with a low lymphocyte count (i.e., less than 500 cells/mm^3).

Anemia

Decreases in hemoglobin levels to less than 8 g/dL were reported in RINVOQ-treated patients in clinical trials.

Evaluate hemoglobin at baseline and thereafter according to routine patient management. Avoid RINVOQ/RINVOQ LQ initiation or interrupt RINVOQ/RINVOQ LQ treatment in patients with a low hemoglobin level (i.e., less than 8 g/dL).

Lipids

Treatment with RINVOQ was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol *[see Adverse Reactions]*. Elevations in LDL cholesterol decreased to pre-treatment levels in response to statin therapy. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Assess lipid parameters approximately 12 weeks after initiation of treatment, and thereafter according to the clinical guidelines for hyperlipidemia. Manage patients according to clinical guidelines for the management of hyperlipidemia.

Liver Enzyme Elevations

Treatment with RINVOQ was associated with increased incidence of liver enzyme elevations compared to treatment with placebo.

Evaluate liver enzymes at baseline and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury.

If increases in ALT or AST are observed during routine patient management and drug-induced liver injury is suspected, RINVOQ/RINVOQ LQ should be interrupted until this diagnosis is excluded.

Embryo-Fetal Toxicity

Based on findings in animal studies, RINVOQ/RINVOQ LQ may cause fetal harm when administered to a pregnant woman. Administration of upadacitinib to rats and rabbits during organogenesis caused increases in fetal malformations. Verify the pregnancy status of patients of reproductive potential prior to starting treatment. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception during treatment with RINVOQ/RINVOQ LQ and for 4 weeks following completion of therapy *[see Use in Specific Populations]*.

Vaccinations

Avoid use of live vaccines during or immediately prior to RINVOQ/RINVOQ LQ therapy initiation. Prior to initiating RINVOQ/RINVOQ LQ treatment, it is recommended that patients be brought up to date with all immunizations, including prophylactic varicella zoster or herpes zoster vaccinations, in agreement with current immunization guidelines.

Medication Residue in Stool

Reports of medication residue in stool or ostomy output have occurred in patients taking RINVOQ. Most reports described anatomic (e.g., ileostomy, colostomy, intestinal resection) or functional gastrointestinal conditions with shortened gastrointestinal transit times. Instruct patients to contact their healthcare provider if medication residue is observed repeatedly. Monitor patients clinically and consider alternative treatment if there is an inadequate therapeutic response.

ADVERSE REACTIONS

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

- Serious Infections *[see Warnings and Precautions]*
- Mortality *[see Warnings and Precautions]*
- Malignancy and Lymphoproliferative Disorders *[see Warnings and Precautions]*
- Major Adverse Cardiovascular Events *[see Warnings and Precautions]*
- Thrombosis *[see Warnings and Precautions]*
- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Gastrointestinal Perforations *[see Warnings and Precautions]*
- Laboratory Abnormalities *[see Warnings and Precautions]*

Clinical Trials Experience

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

Adverse Reactions in Patients with Rheumatoid Arthritis

A total of 3833 adult patients with rheumatoid arthritis were treated with RINVOQ 15 mg or upadacitinib 30 mg tablets once daily in the Phase 3 clinical trials of whom 2806 were exposed for at least one year.

Patients could advance or switch to RINVOQ 15 mg from placebo, or be rescued to RINVOQ from active comparator or placebo from as early as Week 12 depending on the trial design.

A total of 2630 patients received at least 1 dose of RINVOQ 15 mg, of whom 1860 were exposed for at least one year. In trials RA-I, RA-II, RA-III and RA-V, 1213 patients received at least 1 dose of RINVOQ 15 mg, of which 986 patients were exposed for at least one year, and 1203 patients received at least 1 dose of upadacitinib 30 mg, of which 946 were exposed for at least one year.

Table 1: Adverse Reactions Reported in ≥ 1% of Rheumatoid Arthritis Patients Treated with RINVOQ 15 mg in Placebo-controlled Trials

Adverse Reaction	Placebo N = 1042 (%)	RINVOQ 15 mg N = 1035 (%)
Upper respiratory tract infection (URTI)*	9.5	13.5
Nausea	2.2	3.5
Cough	1.0	2.2
Pyrexia	0	1.2

*URTI includes: acute sinusitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, viral upper respiratory tract infection

Other adverse reactions reported in less than 1% of patients in the RINVOQ 15 mg group and at a higher rate than in the placebo group through Week 12 included pneumonia, herpes zoster, herpes simplex (includes oral herpes), and oral candidiasis.

Four integrated datasets are presented in the Specific Adverse Reaction section:

Placebo-controlled Trials: Trials RA-III, RA-IV, and RA-V were integrated to represent safety through 12/14 weeks for placebo (n=1042) and RINVOQ 15 mg (n=1035). Trials RA-III and RA-V were integrated to represent safety through 12 weeks for placebo (n=390), RINVOQ 15 mg (n=385), and upadacitinib 30 mg (n=384). Trial RA-IV did not include the 30 mg dose and, therefore, safety data for upadacitinib 30 mg can only be compared with placebo and RINVOQ 15 mg rates from pooling trials RA-III and RA-V.

MTX-controlled Trials: Trials RA-I and RA-II were integrated to represent safety through 12/14 weeks for MTX (n=530), RINVOQ 15 mg (n=534), and upadacitinib 30 mg (n=529).

12-Month Exposure Dataset: Trials RA-I, II, III, and V were integrated to represent the long-term safety of RINVOQ 15 mg (n=1213) and upadacitinib 30 mg (n=1203).

Exposure adjusted incidence rates were adjusted by trial for all the adverse events reported in this section.

Specific Adverse Reactions

Infections

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, infections were reported in 218 patients (95.7 per 100 patient-years) treated with placebo and 284 patients (127.8 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, infections were reported in 99 patients (136.5 per 100 patient-years) treated with placebo, 118 patients (164.5 per 100 patient-years) treated with RINVOQ 15 mg, and 126 patients (180.3 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Infections were reported in 127 patients (119.5 per 100 patient-years) treated with MTX monotherapy, 104 patients (91.8 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 128 patients (115.1 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Infections were reported in 615 patients (83.8 per 100 patient-years) treated with RINVOQ 15 mg and 674 patients (99.7 per 100 patient-years) treated with upadacitinib 30 mg.

Serious Infections

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, serious infections were reported in 6 patients (2.3 per 100 patient-years) treated with placebo, and 12 patients (4.6 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, serious infections were reported in 1 patient (1.2 per 100 patient-years) treated with placebo, 2 patients (2.3 per 100 patient-years) treated with RINVOQ 15 mg, and 7 patients (8.2 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Serious infections were reported in 2 patients (1.6 per 100 patient-years) treated with MTX monotherapy, 3 patients (2.4 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 8 patients (6.4 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Serious infections were reported in 38 patients (3.5 per 100 patient-years) treated with RINVOQ 15 mg and 59 patients (5.6 per 100 patient-years) treated with upadacitinib 30 mg.

The most frequently reported serious infections were pneumonia and cellulitis.

Tuberculosis

Placebo-controlled Trials and MTX-controlled Trials: In the placebo-controlled period, there were no active cases of tuberculosis reported in the placebo, RINVOQ 15 mg, and upadacitinib 30 mg groups. In the MTX-controlled period, there were no active cases of tuberculosis reported in the MTX monotherapy, RINVOQ 15 mg monotherapy, and upadacitinib 30 mg monotherapy groups.

12-Month Exposure Dataset: Active tuberculosis was reported for 2 patients treated with RINVOQ 15 mg and 1 patient treated with upadacitinib 30 mg. Cases of extra-pulmonary tuberculosis were reported.

Opportunistic Infections (excluding tuberculosis)

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, opportunistic infections were reported in 3 patients (1.2 per 100 patient-years) treated with placebo, and 5 patients (1.9 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, opportunistic infections were reported in 1 patient (1.2 per 100 patient-years) treated with placebo, 2 patients (2.3 per 100 patient-years) treated with RINVOQ 15 mg, and 6 patients (7.1 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Opportunistic infections were reported in 1 patient (0.8 per 100 patient-years) treated with MTX monotherapy, 0 patients treated with RINVOQ 15 mg monotherapy, and 4 patients (3.2 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Opportunistic infections were reported in 7 patients (0.6 per 100 patient-years) treated with RINVOQ 15 mg and 15 patients (1.4 per 100 patient-years) treated with upadacitinib 30 mg.

Malignancies

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, malignancies excluding NMSC were reported in 1 patient (0.4 per 100 patient-years) treated with placebo, and 1 patient (0.4 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, malignancies excluding NMSC were reported in 0 patients treated with placebo, 1 patient (1.1 per 100 patient-years) treated with RINVOQ 15 mg, and 3 patients (3.5 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Malignancies excluding NMSC were reported in 1 patient (0.8 per 100 patient-years) treated with MTX monotherapy, 3 patients (2.4 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 0 patients treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Malignancies excluding NMSC were reported in 13 patients (1.2 per 100 patient-years) treated with RINVOQ 15 mg and 14 patients (1.3 per 100 patient-years) treated with upadacitinib 30 mg.

Gastrointestinal Perforations

Placebo-controlled Trials: There were no gastrointestinal perforations (based on medical review) reported in patients treated with placebo, RINVOQ 15 mg, and upadacitinib 30 mg.

MTX-controlled Trials: There were no cases of gastrointestinal perforations reported in the MTX and RINVOQ 15 mg group through 12/14 weeks. Two cases of gastrointestinal perforations were observed in the upadacitinib 30 mg group.

12-Month Exposure Dataset: Gastrointestinal perforations were reported in 1 patient treated with RINVOQ 15 mg and 4 patients treated with upadacitinib 30 mg.

Thrombosis

Placebo-controlled Trials: In RA-IV, venous thrombosis (pulmonary embolism or deep vein thrombosis) was observed in 1 patient treated with placebo and 1 patient treated with RINVOQ 15 mg. In RA-V, venous thrombosis was observed in 1 patient treated with RINVOQ 15 mg. There were no observed cases of venous thrombosis reported in RA-III. No cases of arterial thrombosis were observed through 12/14 weeks.

MTX-controlled Trials: In RA-II, venous thrombosis was observed in 0 patients treated with MTX monotherapy, 1 patient treated with RINVOQ 15 mg monotherapy and 0 patients treated with upadacitinib 30 mg monotherapy through Week 14. In RA-II, no cases of arterial thrombosis were observed through 12/14 weeks. In RA-I, venous thrombosis was observed in 1 patient treated with MTX, 0 patients treated with RINVOQ 15 mg and 1 patient treated with upadacitinib 30 mg through Week 24. In RA-I, arterial thrombosis was observed in 1 patient treated with upadacitinib 30 mg through Week 24.

12-Month Exposure Dataset: Venous thrombosis events were reported in 5 patients (0.5 per 100 patient-years) treated with RINVOQ 15 mg and 4 patients (0.4 per 100 patient-years) treated with upadacitinib 30 mg. Arterial thrombosis events were reported in 0 patients treated with RINVOQ 15 mg and 2 patients (0.2 per 100 patient-years) treated with upadacitinib 30 mg.

Laboratory Abnormalities

Hepatic Transaminase Elevations

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, alanine transaminase (ALT) and aspartate transaminase (AST) elevations ≥ 3 x upper limit of normal (ULN) in at least one measurement were observed in 2.1% and 1.5% of patients treated with RINVOQ 15 mg, and in 1.5% and 0.7% of patients treated with placebo, respectively. In RA-III and RA-V, ALT and AST elevations ≥ 3 x ULN in at least one measurement were observed in 0.8% and 1.0% of patients treated with RINVOQ 15 mg, 1.0% and 0% of patients treated with upadacitinib 30 mg and in 1.3% and 1.0% of patients treated with placebo, respectively.

In MTX-controlled trials, for up to 12/14 weeks, ALT and AST elevations ≥ 3 x ULN in at least one measurement were observed in 0.8% and 0.4% of patients treated with RINVOQ 15 mg, 1.7% and 1.3% of patients treated with upadacitinib 30 mg and in 1.9% and 0.9% of patients treated with MTX, respectively.

Lipid Elevations

Upadacitinib treatment was associated with dose-related increases in total cholesterol, triglycerides and LDL cholesterol. Upadacitinib was also associated with increases in HDL cholesterol. Elevations in LDL and HDL cholesterol peaked by Week 8 and remained stable thereafter. In controlled trials, for up to 12/14 weeks, changes from baseline in lipid parameters in patients treated with RINVOQ 15 mg and upadacitinib 30 mg, respectively, are summarized below:

- Mean LDL cholesterol increased by 14.81 mg/dL and 17.17 mg/dL.
- Mean HDL cholesterol increased by 8.16 mg/dL and 9.01 mg/dL.
- The mean LDL/HDL ratio remained stable.
- Mean triglycerides increased by 13.55 mg/dL and 14.44 mg/dL.

Creatine Phosphokinase Elevations

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related increases in creatine phosphokinase (CPK) values were observed. CPK elevations > 5 x ULN were reported in 1.0%, and 0.3% of patients over 12/14 weeks in the RINVOQ 15 mg and placebo groups, respectively. Most elevations >5 x ULN were transient and did not require treatment discontinuation. In RA-III and RA-V, CPK elevations > 5 x ULN were observed in 0.3% of patients treated with placebo, 1.6% of patients treated with RINVOQ 15 mg, and none in patients treated with upadacitinib 30 mg.

Neutropenia

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related decreases in neutrophil counts, below 1000 cells/mm^3 in at least one measurement occurred in 1.1% and <0.1% of patients in the RINVOQ 15 mg and placebo groups, respectively. In RA-III and RA-V, decreases in neutrophil counts below 1000 cells/mm^3 in at least one measurement occurred in 0.3% of patients treated with placebo, 1.3% of patients treated with RINVOQ 15 mg, and 2.4% of patients treated with upadacitinib 30 mg. In clinical trials, treatment was interrupted in response to ANC less than 1000 cells/mm^3.

Lymphopenia

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related decreases in lymphocyte counts below 500 cells/mm^3 in at least one measurement occurred in 0.9% and 0.7% of patients in the RINVOQ 15 mg and placebo groups, respectively. In RA-III and RA-V, decreases in lymphocyte counts below 500 cells/mm^3 in at least one measurement occurred in 0.5% of patients treated with placebo, 0.5% of patients treated with RINVOQ 15 mg, and 2.4% of patients treated with upadacitinib 30 mg.

Anemia

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, hemoglobin decreases below 8 g/dL in at least one measurement occurred in <0.1% of patients in both the RINVOQ 15 mg and placebo groups. In RA-III and RA-V, hemoglobin decreases below 8 g/dL in at least one measurement were observed in 0.3% of patients treated with placebo, and none in patients treated with RINVOQ 15 mg and upadacitinib 30 mg.

Adverse Reactions in Patients with Ulcerative Colitis

RINVOQ was studied up to 8 weeks in patients with moderately to severely active ulcerative colitis in two randomized, double-blind, placebo-controlled induction studies (UC-1, UC-2) and a randomized, double-blind, placebo controlled, dose-finding study (UC-4; NCT02819635). Long term safety up to 52-weeks was evaluated in patients who responded to induction therapy in a randomized, double-blind, placebo-controlled maintenance study (UC-3) and a long-term extension study.

In the two induction studies (UC-1, UC-2) and a dose finding study (UC-4), 1097 patients were enrolled of whom 719 patients received RINVOQ 45 mg tablets once daily.

In the maintenance study (UC-3), 746 patients were enrolled of whom 250 patients received RINVOQ 15 mg tablets once daily and 251 patients received RINVOQ 30 mg tablets once daily.

Adverse reactions reported in ≥2% of patients in any treatment arm in the induction and maintenance studies are shown in Tables 2 and 3, respectively.

Table 2: Adverse Reactions Reported in ≥2% of Patients with Ulcerative Colitis Treated with RINVOQ 45 mg in Placebo-Controlled Induction Studies (UC-1, UC-2 and UC-4)

Adverse Reaction	Placebo	RINVOQ 45 mg Once Daily
	N = 378 (%)	N = 719 (%)
Upper respiratory tract infection*	7	9
Acne*	1	6
Increased blood creatine phosphokinase	1	5
Neutropenia*	<1	5
Rash*	1	4
Elevated liver enzymes**	2	3
Lymphopenia*	1	3
Folliculitis	1	2
Herpes simplex*	<1	2

* Composed of several similar terms

** Elevated liver enzymes composed of elevated ALT, AST, GGT, ALP, liver transaminases, hepatic enzymes, bilirubin, drug-induced liver injury and cholestasis.

Other adverse reactions reported in less than 2% of patients in the RINVOQ 45 mg group and at a higher rate than in the placebo group through Week 8 included herpes zoster and pneumonia.

Table 3: Adverse Reactions Reported in ≥2% of Patients with Ulcerative Colitis Treated with RINVOQ 15 mg or 30 mg in the Placebo-Controlled Maintenance Study (UC-3)[1]

Adverse Reaction	Placebo	RINVOQ 15 mg Once Daily	RINVOQ 30 mg Once Daily
	N = 245 (%)	N = 250 (%)	N = 251 (%)
Upper respiratory tract infection*	18	17	20
Increased blood creatine phosphokinase	2	6	8
Pyrexia	3	3	6
Neutropenia*	2	3	6
Elevated liver enzymes**	1	6	4
Rash*	4	5	5
Herpes zoster	0	5	6
Folliculitis	2	2	4
Hypercholesterolemia*	1	2	4
Influenza	1	3	3
Herpes simplex*	1	2	3
Lymphopenia*	2	3	2
Hyperlipidemia*	0	2	2

[1] Patients who were responders to 8 weeks induction therapy with RINVOQ 45 mg once daily
* Composed of several similar terms
** Elevated liver enzymes composed of elevated ALT, AST, GGT, ALP, liver transaminases, hepatic enzymes, bilirubin, drug-induced liver injury, and cholestasis.

The adverse reaction of non-melanoma skin cancer was reported in 1% of patients in the RINVOQ 30 mg group and none of the patients in the RINVOQ 15 mg or placebo group through Week 52.

The safety profile of RINVOQ in the long-term extension study was similar to the safety profile observed in the placebo-controlled induction and maintenance periods.

Overall, the safety profile observed in patients with ulcerative colitis treated with RINVOQ was generally similar to the safety profile in patients with RA and AD.

Specific Adverse Reactions

Serious Infections

Induction Studies: In UC-1, UC-2, and UC-4, serious infections were reported in 5 patients (8.4 per 100 patient-years) treated with placebo and 9 patients (8.4 per 100 patient-years) treated with RINVOQ 45 mg through 8 weeks.

Placebo-controlled Maintenance Study: In UC-3, serious infections were reported in 8 patients (5.9 events per 100 patient-years) treated with placebo, 9 patients (5.0 events per 100 patient-years) treated with RINVOQ 15 mg, and 8 patients (3.7 events per 100 patient-years) treated with RINVOQ 30 mg through 52 weeks.

Laboratory Abnormalities

Hepatic Transaminase Elevations

In studies UC-1, UC-2, and UC-4, elevations of ALT to ≥ 3 x ULN in at least one measurement were observed in 1.5% of patients treated with RINVOQ 45 mg, and 0% of patients treated with placebo for 8 weeks. AST elevations to ≥ 3 x ULN occurred in 1.5% of patients treated with RINVOQ 45 mg, and 0.3% of patients treated with placebo. Elevations of ALT to ≥ 5 x ULN occurred in 0.4% of patients treated with RINVOQ 45 mg and 0% of patients treated with placebo.

In UC-3, elevations of ALT to ≥ 3 x ULN in at least one measurement were observed in 4.4% of patients treated with RINVOQ 30 mg, 2% of patients treated with RINVOQ 15 mg, and 1.2% of patients treated with placebo for 52 weeks. Elevations of AST to ≥ 3 x ULN in at least one measurement were observed in 2% of patients treated with RINVOQ 30 mg, 1.6% of patients treated with RINVOQ 15 mg and 0.4% of patients treated with placebo. Elevations of ALT to ≥ 5 x ULN were observed in 1.2% of patients treated with 30 mg, 0.4% of patients treated with 15 mg, and 0.4% of patients treated with placebo.

Overall, laboratory abnormalities observed in patients with ulcerative colitis treated with RINVOQ were similar to those described in patients with RA.

Adverse Reactions in Patients with Crohn's Disease

RINVOQ was studied up to 12 weeks in patients with moderately to severely active CD in two randomized, double-blind, placebo-controlled induction studies (CD-1, CD-2). Long term safety up to 52 weeks was evaluated in patients who responded to induction therapy in a randomized, double-blind, placebo-controlled maintenance study (CD-3), with additional data provided from a long-term extension (LTE) period.

In the two induction studies (CD-1, CD-2), 1021 patients were enrolled, of whom 674 patients received RINVOQ 45 mg tablets once daily during the placebo-controlled period.

In the maintenance study (CD-3), 673 patients were enrolled, of whom 221 patients received RINVOQ 15 mg tablets once daily and 229 patients received RINVOQ 30 mg tablets once daily during the randomized, placebo-controlled period.

Overall, the safety profile observed in patients with Crohn's disease treated with RINVOQ was consistent with the known safety profile for RINVOQ in other indications.

Adverse reactions reported in ≥2% of patients treated with RINVOQ and at a higher rate than placebo in the induction and maintenance studies are shown in Tables 4 and 5, respectively.

Table 4: Adverse Reactions Reported in ≥2% of Patients with Crohn's Disease Treated with RINVOQ 45 mg in Placebo-Controlled Induction Studies (CD-1 and CD-2)

Adverse Reaction	Placebo	RINVOQ 45 mg Once Daily
	N = 347 (%)	N = 674 (%)
Upper respiratory tract infection*	8	13
Anemia*	6	7
Acne*	2	6
Pyrexia	3	4
Increased blood creatine phosphokinase	1	3
Influenza	1	3
Herpes simplex*	1	3
Leukopenia*	1	2
Neutropenia*	<1	2
Herpes zoster	0	2

* Composed of several similar terms

Adverse reactions reported in less than 2% of patients in the RINVOQ 45 mg group and at a higher rate than in the placebo group through Week 12 included folliculitis, hypercholesterolemia, bronchitis, pneumonia, oral candidiasis, and hyperlipidemia.

Table 5: Adverse Reactions Reported in ≥2% of Patients with Crohn's Disease Treated with RINVOQ 15 mg or 30 mg in the Placebo-Controlled Maintenance Study (CD-3)[1]

Adverse Reaction	Placebo	RINVOQ 15 mg Once Daily	RINVOQ 30 mg Once Daily
	N = 223 (%)	N = 221 (%)	N = 229 (%)
Upper respiratory tract infection*	11	14	12
Pyrexia	2	3	7
Herpes zoster*	2	3	5
Headache*	1	3	5
Acne*	3	2	5
Gastroenteritis*	2	3	3
Fatigue	2	3	3
Increased blood creatine phosphokinase	1	2	3
Elevated liver enzymes[2]	<1	2	3
Leukopenia*	<1	1	2
Neutropenia*	<1	1	2
Bronchitis*	0	1	2
Pneumonia*	1	4	1
Cough	2	3	1

[1] Patients who were responders to 12 weeks induction therapy with RINVOQ 45 mg once daily.
[2] Elevated liver enzymes includes alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, transaminases increased, blood bilirubin increased.
* Composed of several similar terms

Adverse reactions reported in less than 2% of patients in the RINVOQ 15 mg or 30 mg group and at a higher rate than in the placebo group through Week 52 included hyperlipidemia, oral candidiasis, and hypercholesterolemia.

The safety profile of RINVOQ in the long-term extension study was similar to the safety profile observed in the placebo-controlled induction and maintenance periods.

Specific Adverse Reactions

Serious Infections

Induction Studies: In CD-1 and CD-2, serious infections were reported in 6 patients (8 per 100 patient-years) treated with placebo and 13 patients (9 per 100 patient-years) treated with RINVOQ 45 mg through 12 weeks of the placebo-controlled period.

Maintenance Study/LTE: In the long-term placebo-controlled period, serious infections were reported in 10 patients (7 per 100 patient-years) treated with placebo, 7 patients (4 per 100 patient-years) treated with RINVOQ 15 mg, and 13 patients (6 per 100 patient-years) treated with RINVOQ 30 mg.

Gastrointestinal Perforations

Induction Studies: During the induction studies in all patients treated with RINVOQ 45 mg (N=938), gastrointestinal perforation was reported in 4 patients (2 per 100 patient-years). In the placebo-controlled induction period, in CD-1 and CD-2, gastrointestinal perforation was reported in no patients treated with placebo (N=347) and 1 patient (1 per 100 patient-years) treated with RINVOQ 45 mg (N=674) through 12 weeks.

Maintenance Study/LTE: In the long-term placebo-controlled period, gastrointestinal perforation was reported in 1 patient (1 per 100 patient-years) treated with placebo, 1 patient (<1 per 100 patient-years) treated with RINVOQ 15 mg, and 1 patient (<1 per 100 patient-years) treated with RINVOQ 30 mg.

Patients who received placebo or RINVOQ 15 mg for maintenance therapy and lost response were treated with rescue RINVOQ 30 mg (N=336). Among these patients, gastrointestinal perforation was reported in 3 patients (1 per 100 patient-years) through long-term treatment.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors

Upadacitinib exposure is increased when it is co-administered with a strong CYP3A4 inhibitor (such as ketoconazole, clarithromycin, and grapefruit), which may increase the risk of adverse reactions. Monitor patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondylarthritis, pJIA, or giant cell arteritis closely for adverse reactions when co-administering RINVOQ/RINVOQ LQ with strong CYP3A4 inhibitors. Food or drink containing grapefruit should be avoided during treatment with RINVOQ/RINVOQ LQ.

For patients with atopic dermatitis, coadministration of RINVOQ 30 mg once daily with strong CYP3A4 inhibitors is not recommended.

For patients with ulcerative colitis or Crohn's disease taking strong CYP3A4 inhibitors, reduce the RINVOQ induction dosage to 30 mg once daily. The recommended maintenance dosage is 15 mg once daily.

Strong CYP3A4 Inducers

Upadacitinib exposure is decreased when it is co-administered with strong CYP3A4 inducers (such as rifampin), which may lead to reduced therapeutic effect. Coadministration of RINVOQ/RINVOQ LQ with strong CYP3A4 inducers is not recommended.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Surveillance Program

There is a pregnancy surveillance program for RINVOQ/RINVOQ LQ that monitors pregnancy outcomes in women exposed to RINVOQ/RINVOQ LQ. If RINVOQ/RINVOQ LQ exposure occurs during pregnancy, healthcare providers or patients should report the pregnancy by calling 1-800-633-9110.

Risk Summary

Available data from the pharmacovigilance safety database and postmarketing case reports on use of RINVOQ in pregnant women are not sufficient to evaluate a drug-associated risk for major birth defects or miscarriage. Based on animal studies, RINVOQ/RINVOQ LQ has the potential to adversely affect a developing fetus. Advise patients of reproductive potential and pregnant patients of the potential risk to the fetus.

In animal embryo-fetal development studies, oral upadacitinib administration to pregnant rats and rabbits at exposures equal to or greater than approximately 1.6 and 15 times the 15 mg tablet dose, 0.8 and 7.6 times the 30 mg tablet dose, and 0.6 and 5.6 times the maximum recommended human dose (MRHD) of 45 mg (on an AUC basis) resulted in dose-related increases in skeletal malformations (rats only), an increased incidence of cardiovascular malformations (rabbits only), increased post-implantation loss (rabbits only), and decreased fetal body weights in both rats and rabbits. No developmental toxicity was observed in pregnant rats and rabbits treated with oral upadacitinib during organogenesis at exposures approximately 0.29 and 2.2 times the 15 mg dose, 0.15 times and 1.1 times the 30 mg dose, and at 0.11 and 0.82 times the MRHD (on an AUC basis). In a pre- and post-natal development study in pregnant female rats, oral upadacitinib administration at exposures approximately 3 times the 15 mg dose, 1.4 times the 30 mg dose, and the same as the MRHD (on an AUC basis) resulted in no maternal or developmental toxicity *(see Data)*.

The 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. In the U.S. general population, the estimated background risk of major birth defects and miscarriages are 2-4% and 15-20%, 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 inflammatory bowel disease. 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 an oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 5, 25, and 75 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that consisted of misshapen humerus and bent scapula) at exposures equal to or greater than approximately 1.7 times the 15 mg tablet dose, 0.9 times the 30 mg tablet dose, and 0.6 times the MRHD (on an AUC basis at maternal oral doses of 5 mg/kg/day and higher). Additional skeletal malformations (bent forelimbs/hindlimbs and rib/vertebral defects) and decreased fetal body weights were observed in the absence of maternal toxicity at an exposure approximately 84 times the 15 mg dose, 43 times the 30 mg dose, and 31 times the MRHD (on an AUC basis at a maternal oral dose of 75 mg/kg/day).

In a second oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 1.5 and 4 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that included bent humerus and scapula) at exposures approximately 1.6 times the 15 mg dose, 0.8 times the 30 mg dose, and 0.6 times the MRHD (on an AUC basis at maternal oral doses of 4 mg/kg/day). No developmental toxicity was observed in rats at an exposure approximately 0.29 times the 15 mg tablet dose, 0.15 times the 30 mg tablet dose, and 0.11 times the MRHD (on an AUC basis at a maternal oral dose of 1.5 mg/kg/day).

In an oral embryo-fetal developmental study, pregnant rabbits received upadacitinib at doses of 2.5, 10, and 25 mg/kg/day during the period of organogenesis from gestation day 7 to 19. Embryolethality, decreased fetal body weights, and cardiovascular malformations were observed in the presence of maternal toxicity at an exposure approximately 15 times the 15 mg tablet dose, 7.6 times the 30 mg tablet dose, and 5.6 times the MRHD (on an AUC basis at a maternal oral dose of 25 mg/kg/day). Embryolethality consisted of increased post-implantation loss that was due to elevated incidences of both total and early resorptions. No developmental toxicity was observed in rabbits at an exposure approximately 2.2 times the 15 mg tablet dose, 1.1 times the 30 mg tablet dose, and 0.82 times the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

In an oral pre- and post-natal development study, pregnant female rats received upadacitinib at doses of 2.5, 5, and 10 mg/kg/day from gestation day 6 through lactation day 20. No maternal or developmental toxicity was observed in either mothers or offspring, respectively, at an exposure approximately 3 times the 15 mg tablet dose, 1.4 times the 30 mg tablet dose, and at approximately the same exposure as the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

Lactation

Risk Summary

There are no data on the presence of upadacitinib in human milk, the effects on the breastfed infant, or the effects on milk production. Available pharmacodynamic/toxicological data in animals have shown excretion of upadacitinib in milk *(see Data)*. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential for serious adverse reactions in the breastfed infant, advise patients that breastfeeding is not recommended during treatment with RINVOQ/RINVOQ LQ, and for 6 days (approximately 10 half-lives) after the last dose.

Data

A single oral dose of 10 mg/kg radiolabeled upadacitinib was administered to lactating female Sprague-Dawley rats on post-partum days 7-8. Drug exposure was approximately 30-fold greater in milk than in maternal plasma based on AUC_{0-t} values. Approximately 97% of drug-related material in milk was parent drug.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to starting treatment with RINVOQ/RINVOQ LQ *[see Use in Specific Populations]*.

Contraception

Females

Based on animal studies, upadacitinib may cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations]*. Advise female patients of reproductive potential to use effective contraception during treatment with RINVOQ/RINVOQ LQ and for 4 weeks after the final dose.

Pediatric Use

Ankylosing Spondylitis, Non-radiographic Axial Spondyloarthritis, Ulcerative Colitis, and Crohn's Disease

The safety and effectiveness of RINVOQ/RINVOQ LQ in pediatric patients with ankylosing spondylitis, non-radiographic axial spondyloarthritis, ulcerative colitis, or Crohn's disease have not been established.

Geriatric Use

Ulcerative Colitis

Of the 1097 patients treated in the controlled clinical trials, a total of 95 patients with ulcerative colitis were 65 years and older. Clinical studies of RINVOQ did not include sufficient numbers of patients 65 years of age and older with ulcerative colitis to determine whether they respond differently from younger adult patients.

Crohn's Disease

Of the 1021 patients who were treated in the controlled induction clinical trials, a total of 39 patients with Crohn's disease were 65 years of age or older, and no patients were 75 years of age or older. Clinical studies of RINVOQ did not include sufficient numbers of patients 65 years of age and older with Crohn's disease to determine whether they respond differently from younger adult patients.

Renal Impairment

For patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, pJIA, or giant cell arteritis no dosage adjustment is needed in patients with mild (eGFR 60 to < 90 mL/min/1.73 m^2), moderate (eGFR 30 to < 60 mL/min/1.73 m^2), or severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m^2).

For patients with atopic dermatitis, the maximum recommended dosage of RINVOQ is 15 mg once daily for patients with severe renal impairment. No dosage adjustment is needed in patients with mild or moderate renal impairment.

For patients with ulcerative colitis or Crohn's disease, the recommended dosage of RINVOQ for severe renal impairment is 30 mg once daily for induction and 15 mg once daily for maintenance. No dosage adjustment is needed in patients with mild or moderate renal impairment.

RINVOQ/RINVOQ LQ has not been studied in patients with end stage renal disease (eGFR <15 mL/min/1.73m^2). Use in patients with atopic dermatitis, ulcerative colitis, or Crohn's disease with end stage renal disease is not recommended.

Hepatic Impairment

The use of RINVOQ/RINVOQ LQ has not been studied in patients with severe hepatic impairment (Child Pugh C), and is therefore not recommended.

For patients with rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, pJIA, or giant cell arteritis, no dosage adjustment is needed in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment.

For patients with ulcerative colitis or Crohn's disease, the recommended dosage of RINVOQ for mild to moderate hepatic impairment is 30 mg once daily for induction and 15 mg once daily for maintenance.

CLINICAL PHARMACOLOGY

Pharmacokinetics

RINVOQ tablets and RINVOQ LQ are not bioequivalent; therefore, the 2 dosage forms are not interchangeable on a milligram-per-milligram basis.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of upadacitinib was evaluated in Sprague-Dawley rats and Tg.rasH2 mice. No evidence of tumorigenicity was observed in male or female rats that received upadacitinib for up to 101 weeks at oral doses up to 15 or 20 mg/kg/day, respectively (approximately 4 and 10 times the 15 mg tablet dose, 2 and 5 times the 30 mg tablet dose, and 1.6 and 4 times the maximum recommended human dose (MRHD) of 45 mg on an AUC basis, respectively). No evidence of tumorigenicity was observed in male or female Tg.rasH2 mice that received upadacitinib for 26 weeks at oral doses up to 20 mg/kg/day.

Mutagenesis

Upadacitinib tested negative in the following genotoxicity assays: the *in vitro* bacterial mutagenicity assay (Ames assay), *in vitro* chromosome aberration assay in human peripheral blood lymphocytes, and *in vivo* rat bone marrow micronucleus assay.

Impairment of Fertility

Upadacitinib had no effect on fertility in male or female rats at oral doses up to 50 mg/kg/day in males and 75 mg/kg/day in females (approximately 42 and 84 times the 15 mg dose, 22 and 43 times the 30 mg dose, and 16 and 31 times the MRHD, respectively, on an AUC basis). However, maintenance of pregnancy was adversely affected at oral doses of 25 mg/kg/day and 75 mg/kg/day based upon dose-related findings of increased post-implantation losses (increased resorptions) and decreased numbers of mean viable embryos per litter (approximately 22 and 84 times the 15 mg tablet dose, 11 and 43 times the 30 mg tablet dose, and 8 and 31 times the MRHD on an AUC basis, respectively). The number of viable embryos was unaffected in female rats that received upadacitinib at an oral dose of 5 mg/kg/day and were mated to males that received the same dose (approximately 2 times the 15 mg dose, 0.9 times the 30 mg dose, and at 0.6 times the MRHD on an AUC basis).

PATIENT COUNSELING INFORMATION

Advise the patient and caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Serious Infections

Inform patients that they may be more likely to develop infections when taking RINVOQ/RINVOQ LQ. Instruct patients to contact their healthcare provider immediately during treatment if they develop any signs or symptoms of an infection *[see Warnings and Precautions]*.

Advise patients that the risk of herpes zoster is increased in patients taking RINVOQ/RINVOQ LQ and in some cases can be serious *[see Warnings and Precautions]*.

Malignancies

Inform patients that RINVOQ/RINVOQ LQ may increase their risk of certain cancers and that periodic skin examinations should be performed while using RINVOQ/RINVOQ LQ.

Advise patients that exposure to sunlight and UV light should be limited by wearing protective clothing and using a broad-spectrum sunscreen *[see Warnings and Precautions]*.

Major Adverse Cardiovascular Events

Inform patients that RINVOQ/RINVOQ LQ may increase their risk of major adverse cardiovascular events (MACE) including myocardial infarction, stroke, and cardiovascular death. Instruct all patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events *[see Warnings and Precautions]*.

Thrombosis

Inform patients that events of deep venous thrombosis and pulmonary embolism have been reported in clinical trials with RINVOQ. Instruct patients to seek immediate medical attention if they develop any signs or symptoms of a DVT or PE *[see Warnings and Precautions]*.

Hypersensitivity Reactions

Advise patients to discontinue RINVOQ/RINVOQ LQ and seek immediate medical attention if they develop any signs and symptoms of allergic reactions *[see Warnings and Precautions]*.

Gastrointestinal Perforations

Inform patients that gastrointestinal perforations have been reported in clinical trials with RINVOQ and that risk factors include the use of NSAIDs, corticosteroids, or history of diverticulitis. Instruct patients to seek medical care immediately if they experience new onset of abdominal pain, fever, chills, nausea, or vomiting *[see Warnings and Precautions]*.

Retinal Detachment

Inform patients that retinal detachment has been reported in clinical trials with RINVOQ. Advise patients to immediately inform their healthcare provider if they develop any sudden changes in vision while receiving RINVOQ/RINVOQ LQ *[see Adverse Reactions]*.

Laboratory Abnormalities

Inform patients that RINVOQ/RINVOQ LQ may affect certain lab tests, and that blood tests are required before and during RINVOQ/RINVOQ LQ treatment *[see Warnings and Precautions]*.

Vaccinations

Advise patients to avoid use of live vaccines with RINVOQ/RINVOQ LQ. Instruct patients to inform their healthcare practitioner that they are taking RINVOQ/RINVOQ LQ prior to a potential vaccination *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential that exposure to RINVOQ/RINVOQ LQ during pregnancy may result in fetal harm. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions and Use in Specific Populations]*.

Advise females of reproductive potential that effective contraception should be used during treatment and for 4 weeks following the final dose of RINVOQ/RINVOQ LQ *[see Use in Specific Populations]*.

Advise women exposed to RINVOQ/RINVOQ LQ during pregnancy that there is a pregnancy surveillance program that monitors pregnancy outcomes *[see Use in Specific Populations]*.

Lactation

Advise women not to breastfeed during treatment with RINVOQ/RINVOQ LQ and for 6 days after the last dose *[see Use in Specific Populations]*.

Administration

Advise patients that RINVOQ tablets are not substitutable with RINVOQ LQ.

Advise patients not to chew, crush, or split RINVOQ tablets.

For RINVOQ LQ, instruct patients and caregivers to read and follow the Instructions for Use for proper preparation, administration, storage, and disposal.

Advise patients to avoid food or drink containing grapefruit during treatment with RINVOQ/RINVOQ LQ *[see Drug Interactions]*.

Medication Residue in Stool

Instruct patients to notify their healthcare provider if they repeatedly notice medication residue (e.g., intact RINVOQ tablet or fragments) in stool or ostomy output *[see Warnings and Precautions]*.

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Review: EUS techniques expand hepatology toolkit

Although endohepatology offers a potential 'one-stop-shop,' evidence remains heterogeneous and derived from small studies.

By Doug Brunk

Endoscopic ultrasound (EUS)–based interventions are approaching noninferiority to established standards in liver biopsy and may reduce rebleeding in gastric varices, but require further validation, standardization, and cost analyses before widespread adoption, according to a narrative review published in *Gastro Hep Advances*.

For the review, senior author K. Rajender Reddy, MD, of the Division of Gastroenterology and Hepatology at the University of Pennsylvania, and colleagues synthesized emerging data across EUS-guided liver biopsy (EUS-LB), portal pressure gradient measurement (EUS-PPG), gastric varices therapy, elastography, focal liver lesion management, endobariatrics, and liver transplantation applications. They emphasized that although endohepatology offers a potential "one-stop shop," evidence remains heterogeneous and largely derived from small or single-center studies.

EUS-guided liver biopsy: Comparable adequacy, less pain

Liver biopsy remains indicated when diagnostic or prognostic information cannot be obtained by safer alternatives. Contemporary percutaneous liver biopsy (PCLB) demonstrates high adequacy (98% in a large hepatitis B cohort) and low complication rates (1.4% overall), while a systematic review reported a 2.4% incidence of major complications including bleeding (0.48%) and mortality (0.01%).

Against this benchmark, EUS-LB has shown comparable performance in recent randomized trials. Two meta-analyses of four randomized studies cited in the review reported similar diagnostic adequacy between EUS-LB and PCLB when measured by specimen length and complete portal tracts (CPTs), with lower postprocedural pain scores for EUS-LB (standard mean difference −0.58).

A separate systematic review demonstrated pooled histologic diagnostic rates of 93.9% across nine studies. A more recent meta-analysis of five studies reported diagnostic accuracy of 98.6% for PCLB and 88.3% for EUS-LB, though this difference was attributed in part to earlier fine-needle aspiration devices.

Dr. Reddy and coauthors noted that technique refinements, especially use of 19-gauge fine-needle biopsy needles with suction, have improved yield. In a recent multicenter randomized trial, wet suction achieved 99% diagnostic yield and a median of 16 CPTs, outperforming slow-stylet pull in histologic adequacy without increasing adverse events.

EUS-PPG: Direct portal pressure measurement

According to the review, hepatic venous pressure gradient (HVPG) remains the gold standard for portal hypertension assessment. HVPG ≥10 mm Hg defines clinically significant portal hypertension (CSPH); >12 mm Hg predicts variceal bleeding; >16 mm Hg increases mortality risk; and >20 mm Hg independently predicts poor survival. Each 1-mm Hg increase raises mortality risk by 3% in transplant candidates.

EUS-PPG measures pressure directly in the portal vein and can detect pressure changes before the liver (presinusoidal) that HVPG might miss.

Gastric varices: Lower rebleeding with EUS-guided therapy

Cyanoacrylate injection remains standard therapy for gastric varices, achieving primary hemostasis in 8 2%–94% of cases, though rebleeding rates vary widely. A meta-analysis of 24 studies reported pooled recurrence of 34%, early rebleeding 16%, and late rebleeding 39%.

EUS-guided approaches using glue, coils, or both appear to improve outcomes. A systematic review of 23 studies found a pooled treatment efficacy of 93.7%, obliteration rate 84.4%, and early and late rebleeding rates of 7.0% and 11.6%, respectively.

In a separate meta-analysis of six studies, EUS-guided therapy reduced recurrent bleeding and reintervention rates compared with endoscopic glue alone, without differences in pulmonary embolism (OR 0.34), technical success, or mortality.

A randomized trial comparing coil alone vs coil plus glue reported higher immediate obliteration (86.7% vs 13.3%) and lower rebleeding (3.3% vs 20%) with combination therapy.

GI & Hepatology News invited Dr. Reddy to offer additional perspective.

Why is now the right time for this review?

Dr. Reddy: Endohepatology is an evolving field that uses advanced endoscopic techniques to evaluate the liver and biliary tree. While EUS has been available for many years, endohepatology represents an expansion.

Importantly, endohepatology is not a single procedure but a broad diagnostic and therapeutic platform. It encompasses multiple procedures that address various aspects of liver and biliary disease, including tissue acquisition (biopsy), diagnostic assessment, hemodynamic evaluation, and, in selected cases, therapeutic interventions.

How might this review influence clinical practice?

Dr. Reddy: Some may argue that there are already well-established methods for assessing the liver and performing therapeutic interventions. However, in certain clinical scenarios, endohepatology may offer a "one-stop" approach. For example, following liver transplantation, a graft may show signs of dysfunction. In that setting, multiple evaluations are required. We assess the hepatic vasculature to ensure vessel patency, evaluate the liver parenchyma to rule out rejection (often requiring biopsy), and examine the biliary system to exclude strictures or other complications.

Currently, these assessments are often performed in stages — on different days and through separate procedures. As the field advances, endohepatology may allow for a more streamlined, consolidated approach, potentially improving efficiency and patient care.

What gaps in knowledge remain, and what research should be pursued?

Dr. Reddy: Future research must focus on demonstrating that the information obtained through endohepatology is comparable in accuracy to existing standards, while also being less invasive, cost-effective, and efficient.

For example, measurements such as portal pressure gradients are already well established using the transjugular approach. Demonstrating that endoscopic approaches provide equivalent or superior data may be challenging, particularly given the entrenched role of current techniques. Large, well-designed comparative studies will be necessary.

That said, there are areas where endohepatology may offer clear advantages. One example is the management of gastric varices. Emerging studies suggest that endoscopic ultrasound–guided therapies may offer therapeutic benefits over traditional modalities, although this advantage may not yet be widely appreciated.

The challenge lies in generating sufficiently robust evidence to demonstrate superiority over established approaches. However, the potential strength of endohepatology lies in its ability to serve as a "one-stop" platform in selected clinical scenarios, combining diagnostic evaluation and therapeutic intervention in a single setting.

Elastography and focal lesions

Authors of the review characterized EUS shear wave elastography (SWE) as investigational. In a prospective study of 42 patients, area under the curve values for advanced fibrosis were 0.87 (VCTE), 0.80 (left lobe EUS-SWE), and 0.78 (right lobe EUS-SWE). For cirrhosis, AUC values were 0.90, 0.96, and 0.90, respectively.

In focal liver lesions, EUS-guided radiofrequency ablation achieved 100% initial ablation across 25 tumors in 20 patients, though 16% developed local progression and 75% experienced intrahepatic recurrence over 27 months.

Moving beyond the 'one-stop shop'

Despite promising data, the authors caution that robust noninvasive tests for fibrosis and CSPH limit the likelihood that invasive EUS techniques will supplant established tools.

The authors reported having no disclosures.

Global MASH costs set to double by 2040

A multinational modeling study projects sharp rises in advanced liver disease, deaths, and health care spending tied to MASH across nine countries.

By Doug Brunk

Zobair M. Younossi, MD, MPH

Metabolic dysfunction–associated steatohepatitis (MASH) is set to surge by 2040, driving more cases, advanced liver disease, and medical costs that could more than double in most countries without effective intervention, according to a large modeling study spanning nine nations.

For the analysis, published in *Clinical Gastroenterology and Hepatology*, senior author Zobair M. Younossi, MD, MPH, professor and chairman of the Global NASH/MASH Council Center for Outcomes Research in Liver Disease, and colleagues used a country-specific Markov model to project the clinical, economic, and quality-of-life burden of MASH from 2021 to 2040 in the United States, Germany, Spain, France, Italy, the United Kingdom, Japan, Brazil, and Saudi Arabia. Transition probabilities were based on published studies and meta-analyses and then adjusted to match national data on rates of decompensated cirrhosis, liver cancer, and liver transplantation.

Because population-based MASH prevalence data are limited, the researchers used a back-calculation approach to estimate baseline prevalence. They drew from published data on MASH-related cirrhosis prevalence, adjusted for country-specific obesity and type 2 diabetes rates. Incident cases were assumed to enter at early fibrosis stages, reflecting the largely asymptomatic nature of early disease. Mortality estimates were derived using U.S. NHANES-linked data for high-risk metabolic dysfunction–associated steatotic liver disease as a proxy for MASH and applied to country-specific background mortality rates from the Global Burden of Disease study.

Dr. Younossi and coauthors estimated that MASH prevalence would increase in all countries studied, accompanied by a ≥20% rise in advanced liver disease stages, including compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and liver transplantation, driving sharp increases in costs and productivity losses.

In the US, MASH prevalence is projected to rise from 6.71% in 2021 to 7.41% in 2040, translating to an increase from about 17.4 million to 21.8 million affected adults. During the same period, direct annual medical costs are projected to climb from $34.97 billion to $78.59 billion. Comparable trends were projected elsewhere, including Germany ($0.83 billion to $1.82 billion), Spain ($1.48 billion to $3.50 billion), France ($1.28 billion to $2.90 billion), Italy ($1.34 billion to $3.00 billion), the U.K. ($2.18 billion to $5.29 billion), Japan ($1.20 billion to $2.33 billion), Brazil ($3.41 billion to $9.81 billion) and Saudi Arabia ($1.72 billion to $3.96 billion).

The model also projected that work productivity losses would more than double in most countries by 2040. In the United States, productivity losses were estimated to rise from $111.1 billion in 2021 to $246.6 billion in 2040, reflecting both rising prevalence and progression to later disease stages associated with greater functional impairment.

"The consistency of the increasing trends in every country and every region surprised me," Dr. Younossi told *GI & Hepatology News*.

Subgroup analyses highlighted geographic variation in both prevalence and growth rates. Saudi Arabia was projected to have the fastest annual percentage increase in MASH incidence (1.98% from 2021 to 2040), while Japan showed one of the steepest relative increases in prevalence, rising from 3.67% to 5.02%. Across all countries, early-stage MASH prevalence declined slightly as a proportion of total cases, while advanced disease stages increased disproportionately, reflecting aging populations and worsening metabolic risk profiles.

Liver-related mortality was projected to rise steadily. In the United States, liver-related deaths among patients with MASH were estimated to increase from 11.1 to 12.4 per 100,000 between 2021 and 2040. Larger relative increases were projected in Japan, Brazil, and Saudi Arabia, countries with rapidly rising metabolic risk factors.

The authors conducted multiple scenario and sensitivity analyses. A scenario modeling increased use of glucagon-like peptide-1 receptor agonists beginning in 2030, with assumed annual reductions of 1% to 2% in obesity and diabetes prevalence, reduced projected incidence and costs but did not fully offset overall growth in burden. Sensitivity analyses showed that projections were most influenced by assumptions around obesity and diabetes prevalence, disease progression rates, and hospitalization costs.

The analysis had limitations, including reliance on modeled estimates rather than direct longitudinal data, assumptions required to estimate undiagnosed disease, and extrapolation of US-derived mortality risks to other countries.

The researchers were also not able to fully capture future changes in treatment uptake, screening practices and health care delivery, and they reported cost projections in nominal, undiscounted terms. Despite these limits, the authors highlighted the large projected impact.

"Addressing this growing challenge requires not only the development of new therapeutic options but also the implementation of both country-specific and global policy strategies to manage this major noncommunicable liver disease," they wrote. "These strategies should support initiatives to raise public awareness, implement targeted screening for high-risk populations, improve access to health care services, and promote healthy lifestyle changes to combat the global epidemics of obesity and T2D."

Dr. Younossi reported that he is a consultant or has received research funding from Intercept, Cymabay, Boehringer Ingelheim, Ipsen, Gilead Sciences, Inventiva, BMS, GSK, NovoNordisk, Siemens, Madridgal, Merck, Akero, and Abbott. Several coauthors also reported relevant disclosures.

GI & Hepatology News invited Dr. Younossi to comment on the study.

Why does this study matter?

Dr. Younossi: MASH is increasingly recognized as one of the most common liver diseases in the world responsible for a large number of liver cancers, liver transplants and liver deaths. Despite this huge burden, awareness about this disease is suboptimal. This lack of awareness is especially true among policy makers at the national or global level where this liver disease has not been considered as an important non-communicable disease. This analysis assesses the clinical burden, humanistic burden and economic burden of MASLD in 9 countries representing different regions of the world. It shows clearly that without serious policy intervention the comprehensive burden of this disease will be increasing in every region of the world in the next two decades.

How might the findings influence clinical practice?

Dr. Younossi: We are hoping that data like this can influence policy makers to provide resources to deal with this disease by early identification of patients at risk for bad outcomes as well as address some of the environmental drivers of this disease, such as consumption of ultra processed food, high sugary beverages, and lack of physical activity. These interventions can address this disease at a higher level that can then translate into better opportunities for clinicians to offer lifestyle changes to patients with better possibility of success.

What gaps remain, and what research should be done next?

Dr. Younossi: Many other countries are affected by this disease, and we need to understand the projected burden in all settings. Also, we need to show that policy investments can potentially improve outcomes and save both lives and future health care costs for society.

Is there anything else you'd like to say about this work?

Dr. Younossi: In addition to policy changes, there is a need for biopharmaceutical companies to develop better biomarker tests for early identification of at-risk patients and better drug regimens that can be used for those who are at highest risk.

With a little help from my friends: What gastrointestinal pathologists need to know from gastroenterologists

By Raul S. Gonzalez, MD

Pathologists are physicians!

I know, it can be easy to forget this. Pathologists aren't always that visible. Many do not interact with patients, and some only infrequently interact with other physicians. You may not even know where the pathology department at your institution is, and if you do, you may not have visited it. It can be easy to visualize pathology as a "black box": specimen goes in, diagnosis comes out, simple as that.

None of this changes the fact that pathologists are indeed physicians. They understand disease and diagnosis just as much as other physicians. Sending them a specimen is a consultation.

With this in mind, let's consider how gastroenterologists and gastrointestinal pathologists can improve communication for the good of our patients. If an internist sent you a patient and provided absolutely no information, it would be frustrating. If an internist sent many patients to you and simply said "Rule out *H. pylori*" for every single patient, that also leaves room for improvement. Communication between pathologists and clinicians has not received very much attention, [1] but we can use some basic concepts as a start to improving dialogue.

Provide key clinical information

As I already alluded to, communicating what you actually need to know about a patient is very helpful. Writing "rule out celiac" for every single duodenal biopsy is not helpful — trust me, we are already keeping celiac in mind. But if you have a patient who genuinely may have celiac, stating it just that one time alerts the pathologist that this particular patient is at high risk for the disease, and perhaps extra scrutiny is warranted. This also applies to *H. pylori* (we're already looking for the organisms) and Barrett's esophagus (we're already looking for the goblet cells).

Similarly, writing a note with the specimens sent to pathology allows you to communicate important information. Are you worried about graft-versus-host disease? Let the pathologist know the patient had a transplant. Concerned about immune checkpoint inhibitor colitis? Let the pathologist know what medications the patient is taking. Performing surveillance on a rectal scar where a neuroendocrine tumor was previously found? Please write "h/o rectal NET, surveillance." While the pathologist often (but not always) has access to the patient's chart, a simple guiding note will ensure the pathologist understands what you are thinking.

Obtain adequate tissue

Obviously, tissue is sometimes hard to obtain and it's important not to cause too much mucosal damage, but if a pathologist gets a biopsy consisting of half a millimeter of tissue, it's going to be harder to interpret than one with several millimeters. The disease process in question might also go unsampled. In a similar vein — if you suspect a submucosal lesion, performing a biopsy just of the overlying mucosa is unlikely to provide the answer.

Gastric polyps sometimes arise due to various forms of gastritis, [2] so if you sample a gastric polyp, please also send a separate biopsy of the background mucosa. Eosinophilic esophagitis and gastroesophageal reflux disease can look similar microscopically, but the former usually involves the entire esophagus and the latter usually doesn't, so if both are in your differential, please send samples from the proximal, mid, and distal esophagus. [3] Finally, while some specimens require cautery to obtain, the resultant tissue damage can make specimens hard to interpret. Whenever possible, be gentle!

Separate and label specimens when appropriate

If you take several specimens, submit them in separate jars. Placing tissue in the same jar may make it hard to tell what tissue came from where.

One example is colon polyps, which can fragment during the journey. If you need a specific diagnosis for each polyp, they should remain separate. Otherwise, the pathologist may have "three polyps" but 10 tissue fragments, 4 of which are adenomatous and 6 of which are not, making it impossible to tell how many of those endoscopic polyps were truly adenomas. Another example is gastric biopsies taken via the Sydney protocol. If gastric intestinal metaplasia is a concern, submitting each sample in a separate jar makes it easier to tell exactly how widespread the metaplasia should be.

On the topic of gastric biopsies, please label jars with the sample site, as it can be important for the pathologist to know where exactly the tissue originated. This is particularly useful in atrophic gastritis, which makes the oxyntic mucosa resemble antral mucosa. As a result, a biopsy just labeled "stomach" may lead to avoidable errors, such as an antralized portion of fundic mucosa being mistaken for a simply inflamed piece of antral mucosa.

Understand the limitations of pathology

Please be aware when the pathologist is only going to be able to help you so much. This often comes up in the context of biopsies for colitis. Unfortunately, most colitides have overlapping features under the microscope. [4] We can give a differential, but the biopsy is unlikely to provide an answer in the absence of clinical context. There are also diseases that simply do not have microscopic correlates. One example is mast cell activation syndrome. The mast cells in the gastrointestinal tract may be behaving pathologically, but they have the same appearance, quantity, and distribution under the microscope as in people without the syndrome.[5] As much as pathologists would like to provide a definitive answer, performing histochemical or immunohistochemical stains to highlight them does not change this fact. This also applies when a case is challenging microscopically. For any number of reasons, a biopsy can be difficult to interpret. Pathologists don't want to give an equivocal answer if they can avoid it. If cancer is there, we

want to say "positive for malignancy" rather than "atypical and suspicious," but there are times where the latter simply can't be avoided. This may necessitate a conversation and/or repeat sampling.

Contact us

I have saved the most crucial tip for last — get in touch! We also want what's best for our patients and we are happy to discuss an unusual or challenging scenario. Send us an email, give us a call. Even better, set up a time to come by the pathology department, and we can show you the microscope slides and discuss everything together. This also applies when doubt or uncertainty may exist upon reviewing a pathology report. Studies have shown that pathologists and clinicians often communicate differently, and this can lead to different interpretations of reports.[6-8] Most pathologists do try very hard to make their findings and their meaning clear in the reports, but miscommunication can happen. The best way to clear that up is to get in touch with your colleague — the pathologist.

Dr. Gonzalez is Professor of Pathology and Laboratory Medicine at Emory University Hospital, Atlanta, Georgia. He has no relevant conflicts. His X account is @RaulSGonzalezMD.

References

1. *Lehr HA, Bosman FT. Communication skills in diagnostic pathology. Virchows Arch. 2016 Jan. doi: 10.1007/s00428-015-1848-y.*
2. *Vos S, et al. Gastric Epithelial Polyps: When to Ponder, When to Panic. Surg Pathol Clin. 2020 Sep. doi: 10.1016/j.path.2020.05.004.*
3. *Odze RD. Pathology of eosinophilic esophagitis: what the clinician needs to know. Am J Gastroenterol. 2009 Feb. doi: 10.1038/ajg.2008.40.*
4. *Cerilli LA, Greenson JK. The differential diagnosis of colitis in endoscopic biopsy specimens: a review article. Arch Pathol Lab Med. 2012 Aug. doi: 10.5858/arpa.2012-0205-RA. PMID: 22849731.*
5. *Panarelli NC, et al. What Is the Value of Counting Mast Cells in Gastrointestinal Mucosal Biopsies? Mod Pathol. 2023 Feb. doi: 10.1016/j.modpat.2022.100005.*
6. *Powsner SM, et al. Clinicians are from Mars and pathologists are from Venus. Arch Pathol Lab Med. 2000 Jul. doi: 10.5858/2000-124-1040-CAFMAP.*
7. *Mirham L, et al. Addressing the Diagnostic Miscommunication in Pathology. Am J Clin Pathol. 2021 Sep. doi: 10.1093/ajcp/aqab014.*
8. *Battah K, et al. Discrepancies between pathologists and clinicians in interpretation of diagnostic uncertainty in surgical pathology reports. Sci Rep. 2025 Jul. doi: 10.1038/s41598-025-11032-8.*

Green endoscopy: Practical strategies to reduce environmental impact in GI practice

By Rabia de Latour, MD

Background

Health care is a significant contributor to global greenhouse gas (GHG) emissions.

Hospitals, specifically operating rooms and procedural areas are the primary source of health carehealth care-related waste. The U.S. takes the global lead for health care waste production. [1,2] GHG emissions are produced not only from this waste, but also from facility energy usage and the energy required for supply chain.

If global health care were a country, it would be the fifth largest emitter of GHG in the world, making up for about 4.4% of total global emissions.[3] Sustainability efforts to improve emissions and reduce waste within health care are vital to reduce GHG emissions, mitigate the effects of global warming, protect patients from climate change associated health care ramifications, and offer potential cost savings for the institution. According to the *Lancet*, "climate change is the greatest threat to public health."[4]

How to convince stakeholders

Ideally, a stewardship team is set up in each unit to oversee the implemented changes, but also to collect data and report on metrics, particularly cost saving measures and interventions. As not everyone in your clinical administration will prioritize GHG emission reduction, it is extremely important to meet stakeholders *where they are*.

Highlighting the opportunity for cost saving is extremely important to garner support and buy in. Starting with cost saving measures is important to establish "proof of concept" after which other interventions can be considered.

Educational seminars on these interventions and why they matter are also opportunities to educate peers who may not know. Petre et al conducted a study in 2019 interviewing 426 anesthesiologists who reported that despite a 97.5% interest in recycling efforts, only 30.2% did, and the largest reason cited was lack of support (63.5%) and inadequate information and education on the matter (62.8%).[5]

What we can do practically in the GI unit

Procedural areas and operating rooms are prime targets for reducing waste and improving GHG emissions. Listed here are opportunities to improve an endoscopy unit's carbon footprint:

1. **Reprocessing:** A combination of infection control, revenue opportunity, and difficult logistics with reprocessing had moved the field of medicine largely towards single use disposable medical devices. Non-invasive items like pulse oximeters, sequential compression device (SCD boots), and electrocardiogram (EKG) leads are often utilized as "single use" and disposed, immediately going to landfill. Industry partners now offer the opportunity sell back these items for reprocessing, with an opportunity to generate revenue for the hospital.[6,7] Hospital systems can decide if they would like to purchase reprocessed items (or not). This opportunity serves as a great "starter" option for hospital systems.

2. **Waste allocation:** Regulated medical waste (RBW) also known as "red bag waste" is potentially infectious or hazardous hospital waste that can serve as a potential threat to the handler or the population living within proximity to the allocated landfill. As such, it is handled in specific (red) bags and often driven far distances to be incinerated. Not only does this waste cost more to be handled and disposed of,[8,9] but the incineration process is hazardous to the community. The CDC has designated an appropriate amount of RBW to be 3-5% of a hospital's waste, but due to poor education on what exactly goes into the red bins, many health care providers overutilize the bins.[10] Educational initiatives on appropriate use of the bins and associated sharps containers can be offered free of charge by sustainability working groups within the hospital or ambulatory facility. Gastroenterology-specific guidelines have been published to guide on what items warrant placement within the red bins and sharps containers.[11] Generally, containers with free-flowing blood or blood products and items completely saturated with blood are some examples of procedural waste items that require placement into the red bins.[12] It is equally as important to educate clinicians on the items that do not go into the bin, including gowns, gloves, and gauze unless grossly bloody.

3. **Reduction in unnecessary procedures:** While often not the most popular item for providers who work in private practice or productivity-based systems, the reality is that each procedure of the average 18 million endoscopies performed annually within the United States has a carbon footprint, and not all are necessary. Reducing interventions such as endoscopy through non-invasive screening methods in average-risk individuals provide excellent opportunities to reduce the carbon footprint of endoscopy.

4. **Non-sterile water:** There is no direct evidence proving the need for sterile water during routine endoscopy.[13] There is an ongoing push within the community of sustainability advocates to normalize the use of tap water for lavage during routine endoscopy.[14]

5. **Reusable gowns:** Reusable gowns are an excellent opportunity to reduce the GHG emissions from an endoscopy unit and reduce costs. A hospital system that transitioned to

reusable gowns reported a $60,000 decrease in cost and 50,000 pound reduction in waste.[10,12]

6. **Endoscopic decontamination/processing:** Reusable scopes require decontamination. Alternative, ecofriendly, green options for cleaning solutions offer excellent options.

7. **Resect and discard:** Not all pathology specimens require formal pathology evaluation to change clinical management. An example being hyperplastic polyps within the distal, left colon. Additional interventions include separately sending tubular adenomas throughout the colon that have identical pit patterns suggesting their degree of adenomatous change. The "resect and discard" method for removing pre-cancerous small lesions with predicable pathology results is an excellent opportunity to reduce the carbon footprint.

8. **Recycling:** Recycling non-soiled rigid plastic waste can divert it from landfill.[15,16] Collaborating with industry to push for biodegradable packaging or recyclable packaging remains an opportunity.[16] In the interim, working within your facility to recycle rigid plastic and cardboard boxes remains an opportunity to reduce waste.

9. **Double-sided printing:** Hospitals continue to print an exorbitant amount of paperwork. Recycled paper is an option.[17]

10. **Lighting:** Placing light emitting diode (LED) lighting, ideally with motion sensors creates an opportunity to reduce emissions created by unnecessary lighting of units during "off hours. If such upgrades are not possible, enacting a "lights off initiative" during "off" hours is an alternative.[12]

Conclusion

Improving our efforts in reducing carbon emissions serve our patients and our communities, all while offering potential cost saving opportunities. Straight forward, attainable opportunities to achieve this goal, as outlined in this paper, present an opportunity to enact change.

References are available in the online version of the article.

Rewriting the gut–brain story with Dr. Trisha Pasricha

The BIDMC Gut-Brain Institute director blends research, journalism, and stigma-busting education.

By Sierra Rendon

Trisha Pasricha, MD, MPH, has intentionally built a career at the intersection of rigorous science and fearless communication. As director of the BIDMC Gut-Brain Institute, the physician-scientist is advancing understanding of the cellular and molecular mechanisms that connect the gut and brain — including groundbreaking work exploring the gut-first origins of Parkinson's disease. Her NIH-funded research examines how gastrointestinal symptoms may precede neurologic disease by years, potentially opening the door to earlier detection and intervention.

But Dr. Pasricha's influence extends far beyond the laboratory. As the widely read "Ask a Doctor" columnist for *The Washington Post*, she tackles readers' most pressing — and often most embarrassing — health questions with clarity, humor, and unwavering scientific rigor. Her forthcoming book, "You've Been Pooping All Wrong" (Avery/Penguin Random House, April 2026), aims to normalize conversations around bowel health while grounding advice in peer-reviewed research.

Whether mentoring the next generation of neurogastroenterologists, investigating biomarkers of disease during routine colonoscopy, or challenging myths about what constitutes "normal" bowel habits, Dr. Pasricha is reshaping how patients and physicians think about the gut. In this month's Member Spotlight, she reflects on science communication, stigma, and the future of the gut–brain axis.

"If we don't meet people where they are, they'll find answers elsewhere — and not always from credible sources."

What inspired you to start writing an "Ask a Doctor" column, and how has that experience changed the way you approach patient education?

Dr. Pasricha: I had always loved medical journalism. In college, I interned at the CNN medical unit in Atlanta and later worked for ABC News in New York before GI fellowship. But I had taken a bit of a break from it because of medical training — which, as everyone knows, is truly all-consuming. When the COVID-19 pandemic hit, I saw firsthand the enormous scale of misinformation and how dire the consequences could be. I spent a lot of time thinking about the role science communication plays and how we could be engaging yet unwaveringly grounded in truth. I was post-call from a shift on the COVID wards in the early days of spring 2020 when I wrote an op-ed for CNN about my experience on the front lines. It was the first time I had written for the media in years, and the response was incredible.

Even once I returned to writing more regularly after the pandemic, the landscape of medical information had changed. I saw patients in clinic who had been suffering for years with symptoms they were too embarrassed to discuss. They were getting all their information online.

The column gave me a way to reach people before they walked into an exam room — to normalize the questions they were afraid to ask. I've learned that humor goes a long way in helping people remember important information. If you can make someone laugh about their bowel habits, they're far more likely to follow your advice. I don't answer personal medical questions in the column, but I address the kinds of questions people want answered but may not have time to discuss during a 15-minute visit — questions like, "Are creatine supplements worthwhile?" or "Why are more young people getting cancer?" If we don't meet people where they are, they'll find answers elsewhere — and not always from credible sources.

Your new book, "You've Been Pooping All Wrong," is slated for release this month. What made you want to write a book about bowel and gut health, and what do you hope readers get from it?

Dr. Pasricha: About one in three people avoid talking to their doctor about bowel symptoms because of embarrassment. We've been conditioned since potty training not to talk about what happens in the bathroom. It became taboo, which is why I found so many adults entering my clinic unsure of what normal bowel habits actually look like, much less how to optimize their gut health. That silence makes us sicker.

I wrote "You've Been Pooping All Wrong" to give people permission to pay attention to their gut — and to arm them with the science to understand what's happening. I hope readers feel empowered, less embarrassed, and maybe even excited about their bodies.

You've built a reputation for tackling "embarrassing" topics with humor and clarity. How do you balance scientific rigor with accessibility when explaining complex GI health issues?

Dr. Pasricha: The science has to be rock-solid — that's nonnegotiable. But the delivery is where you can have fun. I think of myself as a translator: my job is to take complex research and turn it into something patients, readers, or viewers

Below: Dr. Pasricha with her chow chow, Cannoli.
Top Right: Dr. Pasricha speaking about colorectal cancer screening at the Boston Globe Future of Medicine Summit in 2025.
Bottom Right: Outside The Washington Post building in Washington, D.C, where she serves as a columnist.
Far Bottom Right: Filming an on-camera television interview about women's health.

can use. Humor lowers defenses and makes people lean in. If someone is laughing about "poophoria," they're also learning about the vagus nerve and the enteric nervous system. That principle guided my book: every chapter is grounded in peer-reviewed research but wrapped in practical tools and humor that make it hard to put down.

Your work bridges clinical medicine, research, and public communication. How does your role as a medical journalist influence your research, and vice versa?

Dr. Pasricha: They feed each other in surprising ways. Writing for a public audience forces me to ask: Why does this research matter to a real person? How will it change daily habits? As someone who works in both basic science and clinical trials, I understand why certain studies can or cannot be done. That helps me contextualize findings for readers — where the limits are and why even imperfect studies can be illuminating.

The joy of my work is that it's a two-way street. Reader questions shape my research. For example, my study on smartphone use and hemorrhoid risk came directly from a reader question and generated real data on a topic no one had studied. The book is the culmination of that feedback loop — bringing together lessons from patients, readers, and the lab.

The book explores the brain–gut–microbiome connection. Can you share one surprising insight?

Dr. Pasricha: One insight that surprises many people is that Parkinson's disease may begin in the gut, not the brain. Pathology can appear in the gut's nervous system years — even decades — before classic neurological symptoms develop. These gastrointestinal symptoms are the focus of my K23 grant from NIDDK and a major section of the book. The gut truly functions as a "second brain," and what happens in the intestines can affect the entire body.

You'll be hosting an author Q&A event at AGA Central during Digestive Disease Week® (DDW) this year. What can attendees expect to hear from you?

Dr. Pasricha: I'm thrilled to be joined by my father, Dr. Pankaj Jay Pasricha, a leader in neurogastroenterology. We'll tackle common gut health myths from a Boomer-versus-Gen Z perspective — part science, part family debate. We'll cover everything from daily bowel habits to probiotics and where the science stands. I'll also have copies of "You've Been Pooping All Wrong" available.

In 2022, you received an AGA Research Scholar Award. How did that shape your trajectory?

Dr. Pasricha: The award was transformative. It gave me the runway and credibility to pursue long-term questions about the gut-brain connection. That support directly enabled my NIH-funded lab studying GI symptoms in neurodegenerative diseases. I'm grateful to AGA for investing in me early, and I hope to mentor the next generation of neurogastroenterologists.

What's a common misconception about GI health?

Dr. Pasricha: That you have to poop every day to be healthy. Normal ranges from three times a day to three times a week. What matters is what's comfortable for you and whether changes affect your quality of life.

Looking ahead, what excites you most?

Dr. Pasricha: The evolving landscape of science communication both excites and concerns me. There's enormous public appetite for health information, but also widespread oversimplification and misinformation. The challenge is making nuance compelling. It's easy to go viral with a hot take; it's harder to say, "We don't fully understand this yet." But that's what people need. I want to keep building something where nuance is the feature, not the liability.

Lightning round

Tell us about a mentor and what you learned from them.

My dad — he taught me how to think like a scientist.

Who inspires you?

My toddlers.

What are you excited about working on right now?

My book launches April 7.

Best piece of advice you've given or received?

If not now, then when?

Favorite quote or words to live by?

Do your best for the right reasons.

What's your secret talent?

I'm devastatingly good at video games.

If you were not a GI, what would you be?

Bollywood film director.

What's your favorite GI organ:

The stomach.

Favorite way to spend a day off?

Cuddling my chow chow, Cannoli, and taking my kids to the beach.

Best way to unwind after work?

Going to the gym with my husband.

YOU CAN'T TRUST IgG4-RD TO RESPECT BOUNDARIES

Immunoglobulin G4-related disease (IgG4-RD) is a chronic, systemic, immune-mediated disorder that can manifest in nearly any organ.[1]

- By the time IgG4-RD is diagnosed, patients have **3 affected organs** on average[2]

- Within 3 years of any flare, **up to 90% of patients** will experience flare recurrence in the same affected organ or at a different anatomical site[3]

EXAMPLE PATIENT CASE

PANCREATOBILIARY INVOLVEMENT

Presentation

A 66-year-old patient presents with painless obstructive jaundice.

Potentially misdiagnosed as:

Pancreatic cancer, cholangiocarcinoma, primary sclerosing cholangitis

Diagnostic workup

Serology: Elevated IgG4 levels

Imaging: Diffuse pancreatic enlargement, biliary strictures, and enlarged lymph nodes in abdomen

Pathology: EUS-guided core biopsy of the pancreas showing a small vein surrounded by lymphoplasmacytic inflammation

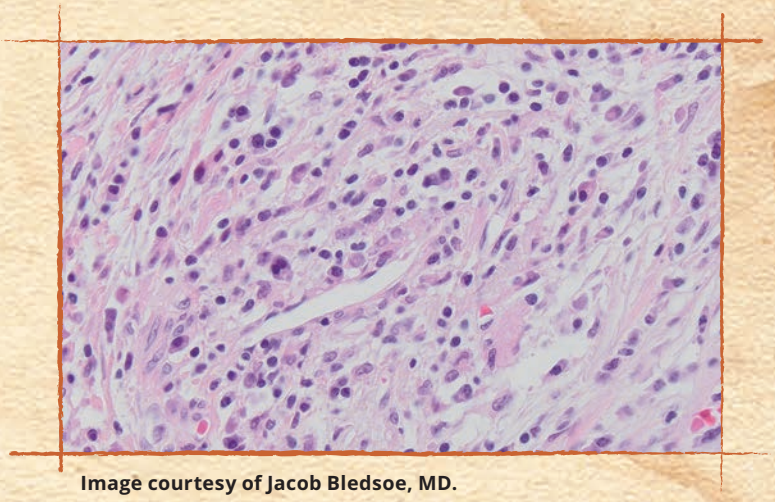

Image courtesy of Jacob Bledsoe, MD.

Biopsy of the pancreas.

Steroid trial

Responsive

Diagnosis

Type 1 autoimmune pancreatitis (IgG4-related pancreatitis) and IgG4-related cholangitis

Know when IgG4-RD belongs on your differential

Scan the code or visit IgG4related.com to learn more

IgG4-RD ICD-10 code: D89.84*

*This information is provided for educational purposes only. It is the responsibility of the healthcare provider to select the proper codes and ensure the accuracy of all statements used in seeking coverage and reimbursement for an individual patient.

EUS, endoscopic ultrasound; ICD, International Classification of Diseases.

References: 1. Katz G, Stone JH. *Annu Rev Med*. 2022;73:545-562. **2.** Yamada K, Yamamoto M, Saeki T, et al. *Arthritis Res Ther*. 2017;19:262. **3.** Lanzillotta M, Mancuso G, Della-Torre E. *BMJ*. Published online June 16, 2020:m1067.

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