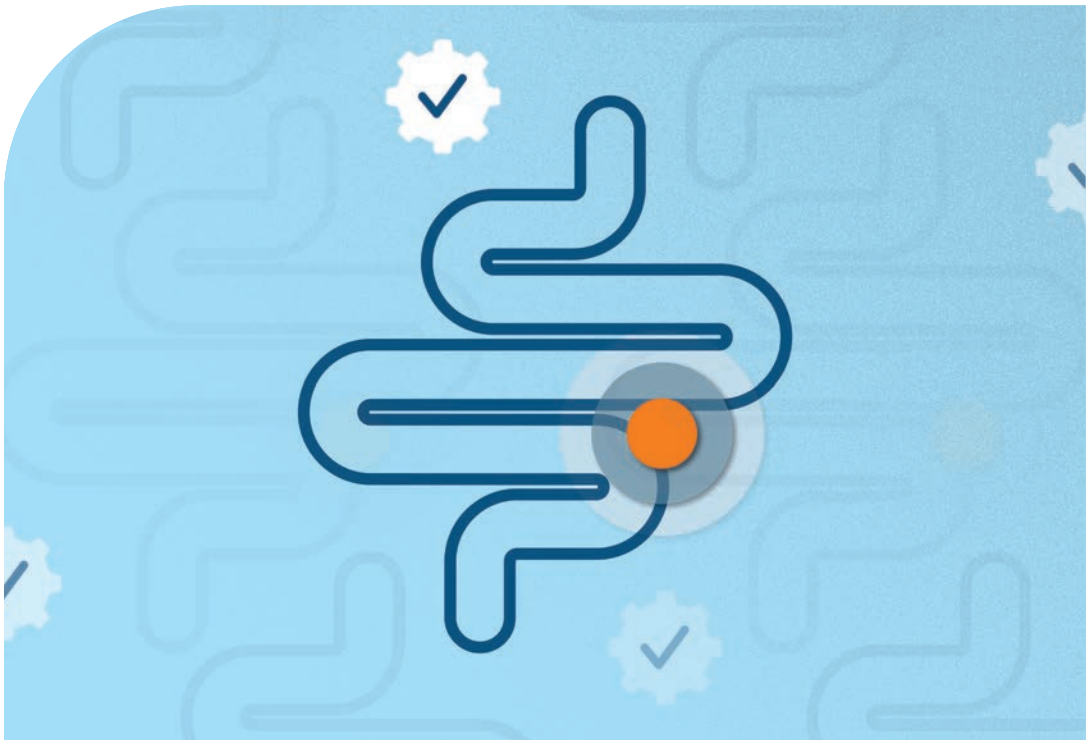
GI&Hepatology News

American Gastroenterological Association's official newspaper



AGA unveils new clinical practice guideline for Crohn's disease

The guideline offers practice-ready implementation and two clinical decision support tools that may help navigate treatment choices.

By Doug Brunk

AGA has rolled out a new living clinical guideline to steer the pharmacologic management of moderate-to-severe Crohn's disease, prioritizing early use of advanced therapies over step-up strategies that begin with corticosteroids or immunomodulators.

The update was prompted by the approval of new advanced therapies for Crohn's disease since the publication of the previous AGA guidelines for moderate-to-severe active disease in 2021, according to the guideline's first author Frank I. Scott, MD, MSCE, of the Crohn's and Colitis Center and the Division of Gastroenterology and Hepatology at the University of Colorado Anschutz School of Medicine in Aurora. "These guidelines highlight that there are now multiple treatment options to consider for patients for managing their moderate to severely active Crohn's disease," Dr. Scott told *GI & Hepatology News*. "We hope that they will help clinicians determine how to maximize the potential benefit of the full armamentarium of therapies available to treat this disease."

For this guideline update, published in *Gastroenterology*, a 10-member panel conducted a network meta-analysis to compare 11 medications and used the GRADE framework to evaluate evidence certainty and craft graded clinical recommendations.

Continues · Page 7

Mediterranean diet beats traditional dietary advice in IBS

Among adults with irritable bowel syndrome, a randomized UK trial found the Mediterranean diet outperformed traditional dietary advice, achieving symptom improvement rates comparable to low FODMAP therapy, while being easier to implement and offering broader, well-established health benefits overall outcomes.

Read More • Page 9

Ranitidine's return 'unlikely to provide greater clinical benefit'

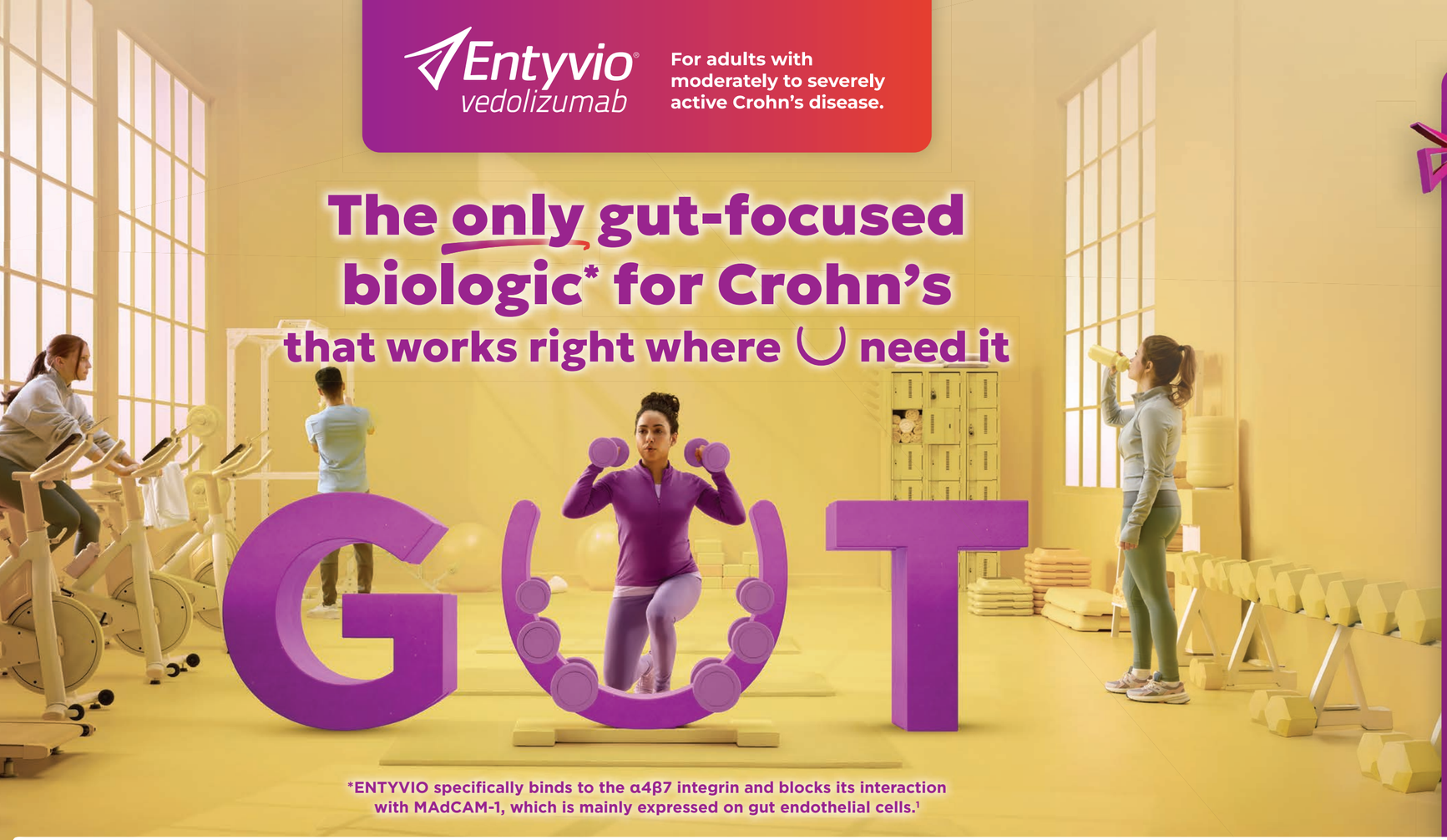
The FDA approved a reformulated ranitidine tablet, returning the H2 blocker to the US market after 5 years, with new controls preventing a potential carcinogen formation. Experts note it offers no clear advantage over famotidine, and switching should be individualized based on symptoms.

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]

Results U 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.

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.

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 U 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

A year of transitions

Nineteen years ago, in January 2007, the first issue of *GI & Hepatology News*, AGA's official newspaper, was published. While the newspaper has evolved significantly since that time in style and content, its core focus on communicating current news and emerging trends and technologies in gastroenterology, particularly as they impact clinical care, has remained.

This year marks a year of transition for the newspaper as it continues to evolve to best serve the needs of its readership. First, starting with our January issue, we welcome a new publisher (Conexiant), bringing fresh ideas (including my new avatar), the opportunity to collaborate on innovative initiatives, and to consider new ways to serve the modern reader. Conexiant runs a large medical news operation, with experience producing and syndicating content across more than 12 specialties. They have a deep GI and hepatology reach and share our commitment to providing easy access to the most important clinical news.

Later this year, as the current leadership concludes its 5-year term, GIHN also will welcome a new editor and editorial board, marking another major transition. For those interested, details on how to apply will be available this spring, so stay tuned! I strongly encourage you to consider this exciting opportunity to shape the next 5 years of the newspaper and ensure its continued success. If you'd like to be notified when the application opens, please email ginews@gastro.org.

In this issue, we highlight AGA's new living clinical practice guideline on pharmacologic management of moderate-to-severe Crohn's disease, as well as a recent RCT from *Annals of Internal Medicine* demonstrating the superiority of the Mediterranean diet to traditional dietary advice in treating IBS-related symptoms. In this month's Member Spotlight, we feature Dr. Richa Shukla, who shares insights on how she combines her passions in IBD, women's health, and medical education and manages competing priorities at work and at home. In this month's AGA Perspectives column, we highlight the evolving role of gastroenterologists in obesity management, from prescribing and supporting use of GLP-1RAs to performing endoscopic weight loss procedures such as ESG.

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

Honoring a legacy

By John Allen, MD, AGAF

Kim Isaacs, MD, passed peacefully on Thanksgiving Day, surrounded by her family. On behalf of AGA, we extend our heartfelt condolences. "Dr. Kim" served on the editorial board of *GI and Hepatology News* when I was Editor-in-Chief from 2016 to 2022. I found her thoughtful presence and expertise to be invaluable during our time guiding the publication.

A professor of medicine and co–director of the Multidisciplinary Inflammatory Bowel Disease Center at the University of North Carolina at Chapel Hill, she was an internationally recognized expert in inflammatory bowel disease (IBD), with special interests ranging from pregnancy and IBD to the effects of the Affordable Care Act on patients. She was active in AGA, contributing through multiple leadership and mentoring roles.

At the University of North Carolina, she was a treasured physician, teacher, mentor, and researcher. She completed her gastroenterology fellowship training there in 1991 and then spent 42 years at UNC caring for countless patients, teaching generations of students and fellows, and publishing research that changed the care of patients with IBD. The numerous honors bestowed on her at UNC and nationally are a testament to her passion for teaching and patient care.

Her leadership was exceptional, demonstrated by the many positions of responsibility she fulfilled at for the Crohn's & Colitis Foundation.

Her research contributions were equally impactful. She participated in more than 75 funded grants pivotal to the care of patients with IBD and served as principal investigator for nearly 50. Her contributions to clinical care will continue long into the future.

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"I have never encountered a class of medications where patients are more willing to tolerate said side effects and persevere than when prescribing GLP1-RAs."

Dr. Marianna Papademetriou • Perspectives • See Page 18

AGA unveils new clinical practice guideline for Crohn's disease

Continued From Page 1

Of the 16 evidence-based recommendations, the panel rated one as "strong," nine as "conditional," and six as "knowledge gaps." In the guideline, the word recommends denotes a strong recommendation, whereas suggests signifies a conditional one. Key highlights include the following:

- AGA recommends infliximab, adalimumab, ustekinumab, risankizumab, mirikizumab, guselkumab, or upadacitinib, and suggests certolizumab pegol or vedolizumab over no treatment.
- For patients who are new to advanced therapies, AGA recommends initiating treatment with higher-efficacy agents — such as infliximab, adalimumab, vedolizumab, ustekinumab, risankizumab, mirikizumab, or guselkumab — rather than lower-efficacy options like certolizumab pegol or upadacitinib.
- For patients previously treated with advanced therapies, preferred options include higher- or intermediate-efficacy medications such as adalimumab, risankizumab, guselkumab, upadacitinib, ustekinumab, or mirikizumab, rather than a lower-efficacy medication such as vedolizumab or certolizumab pegol.

The guideline panel also advises using combination therapy with a thiopurine when considering using infliximab, and that in individuals who achieve steroid-free remission with such therapy, providers can consider withdrawing the immunomodulator.

"Importantly, these guidelines should be viewed as general recommendations, and we advocate that clinical decisions should be between providers and their patients when making treatment decisions," Dr. Scott noted. "Shared decision-making is critical."

To make the recommendations easy to use, the guideline offers practice-ready implementation considerations and two clinical decision support tools that help clinicians navigate pharmacologic treatment choices.

Dr. Scott noted that the guideline recommendations regarding the withdrawal of immunomodulators in patients receiving combination therapy with an anti-TNF and an immunomodulator who have achieved remission for more than 6 months will likely influence his practice. "This was something I'd often discussed with patients when starting combination therapy, but I think with the significant volume of data supporting this recommendation in these guidelines, I will address this more frequently in appropriate patients," he said.

Dr. Scott added that, unexpectedly, the panel was unable to offer a recommendation regarding treatment to a target of mucosal healing. "This target conceptually makes sense, but prospective clinical trial data supporting this approach, over targeting clinical remission, unfortunately are currently limited," he explained. "There are several ongoing clinical trials assessing this endpoint, however, and we hope that future versions of these guidelines can make a formal recommendation regarding targeting mucosal healing. The benefit of our living guideline approach is that as these data become available, we will be able to incorporate them more rapidly."

The panel identified several critical knowledge gaps, including the role of combination therapy for non-TNF biologics as well as whether targeting endoscopic remission (as opposed to clinical remission) yields additional benefit. They also recognized gaps in the research. For example, "the appropriate timing and frequency of endoscopic evaluation, as well as its relation to clinical outcomes, including medication persistence, maintenance of remission, and reduction of CD-related adverse events is unclear at this time, and there is significant heterogeneity regarding time to achieving endoscopic healing or other structural outcomes," the panel members wrote. "Understanding not only these temporal associations between treatment duration and structural assessment, but also the factors that might predict an expected earlier or later response is critical; such predictive models would allow clinicians to select the appropriate assessment window and modify current therapies more accurately."

In contrast to other society guidelines, AGA guideline panel members "felt it was appropriate to use current state-of-the-art synthesis methods to attempt to provide clinicians with guidance in relation to positioning these therapies in treatment-naïve and treatment-exposed individuals," they wrote. The guidelines are living documents that "will be updated quarterly, allowing for rapid evolution as new data become available."

The guideline highlights the treatment options with the strongest evidence, taking each patient's prior treatment experience into account. "I think it's important to emphasize that treatment decisions should be individualized and should involve shared decision-making among providers and their patients," Dr. Scott said. "Patient preferences, age, active comorbidities, and pregnancy considerations should always be considered when selecting the appropriate treatment plan for our patients."

Dr. Scott disclosed that he has received honoraria from AGA, Crohn's and Colitis Foundation, Medscape/WebMD, and MedPage Today. He has also received research support from the Crohn's and Colitis Foundation.

Victor G. Chedid, MD, a gastroenterologist at the Mayo Clinic in Rochester, Minnesota, discussed the importance of the guidelines in an interview with *GI & Hepatology News.*

In your opinion, what are the top three recommendations from this guideline?

Dr. Chedid:

- Early initiation of advanced therapies rather than step-up therapy or immunomodulator-only strategies for moderate to severe Crohn's disease.
- First-line therapy in advanced-therapy–naïve patients should use higher-efficacy medications (infliximab, adalimumab, vedolizumab, ustekinumab, risankizumab, mirikizumab, guselkumab) over lower-efficacy medications (certolizumab pegol or upadacitinib).
- Although immunomodulator monotherapy is discouraged for induction of remission, combination therapy with an immunomodulator is suggested only when using infliximab in individuals naïve to thiopurines to optimize outcomes.

Are there specific recommendations in the guideline that surprised you?

Dr. Chedid: One notable aspect is the guideline's positioning of upadacitinib. For advanced-therapy–naïve patients, it is grouped with certolizumab pegol as a lower-efficacy medication. However, for patients with prior exposure to advanced therapies, upadacitinib is considered higher efficacy, while certolizumab pegol and vedolizumab remain lower efficacy.

In October 2025, the FDA updated upadacitinib's labeling. Previously, treatment required failure or intolerance to an anti-TNF agent. The updated labeling allows its use after inadequate response to one approved systemic therapy, provided anti-TNF therapy is clinically inadvisable.

AGA's classification stems from three randomized controlled trials showing that upadacitinib was highly effective for isolated colonic Crohn's disease but not significantly effective for ileal disease, leading to its lower-efficacy designation for advanced-therapy–naïve patients.

Why is now a good time for publication of this guideline? What gap(s) in knowledge or therapeutics does it seek to fill?

Dr. Chedid: The timing reflects a rapidly evolving therapeutic landscape in the management of moderate to severe Crohn's disease. Since the last AGA guideline in 2021, four new advanced therapies have been approved, nearly doubling available treatment options. This guideline addresses the need for clear, evidence-based positioning of these novel therapies and provides strong support for moving away from traditional "step-up" strategies reliant on corticosteroids or slow-acting immunomodulators.

Dr. Chedid disclosed that he serves as the as Principal Investigator for a Pfizer-funded study on LGBTQ+ health and IBD. He also provides consulting for Takeda on educational programs related to LGBTQ+ health and IBD, and for PRIME Education on CME activities focusing on the same.

Ranitidine's return 'unlikely to provide greater clinical benefit'

New formulation incorporates stronger manufacturing controls and stability measures to prevent a potential carcinogen from forming.

By Doug Brunk

The FDA recently approved a newly reformulated ranitidine tablet, allowing the H2 receptor blocker to return to the U.S. market after 5 years. The previous version was removed in 2020 because N-nitrosodimethylamine (NDMA), a potential carcinogen, could form in the product over time. The new formulation incorporates stronger manufacturing controls and stability measures to prevent NDMA from forming during storage.

Ranitidine has been used to treat GERD, peptic ulcers, and conditions with excess acid production such as Zollinger–Ellison syndrome. The FDA reported that the reformulated product works the same as earlier approved versions and offers the same expected clinical benefit.

According to Binu V. John, MD, AGA spokesperson and Chief of Gastroenterology and Hepatology at the Miami VA Health System, since the withdrawal, most patients were switched to famotidine, a medication with an identical mechanism of action and without similar concerns. "Famotidine at doses of 20 mg is equivalent in potency to the clinically recommended dose of 150 mg of ranitidine," Dr. John said. "Additionally, famotidine has a longer half-life, and unlike ranitidine, does not have Drug interactions with medications metabolized by the P450 enzymes. Therefore, the availability of ranitidine back in the market is unlikely to provide a greater clinical benefit over current options."

Binu V. John, MD

The FDA recommends that any switch to ranitidine from another medication should be guided by the patient's current symptom control, risk factors, and overall treatment plan. The new formulation also comes with updated storage instructions, which are important for keeping the product stable and preventing NDMA formation.

To maintain safety and product quality, the FDA highlighted several key steps that patients and clinicians should follow:

- Keep ranitidine tablets in the original bottle and protect the bottle from moisture.
- After opening the bottle for the first time, discard any remaining tablets after 90 days, or by the expiration date — whichever comes first.
- If multiple bottles are dispensed, open only one at a time; keep the others sealed until needed.
- Remove just one tablet per dose and secure the bottle immediately.
- Do not remove the desiccant; it must stay in the bottle.

"While it is beneficial to have an alternative drug available for patients, both medications work by the same mechanism and ranitidine does not offer advantages over famotidine," Dr. John said. "The major downside of medications in this class is tachyphylaxis, where these medications lose potency after 6 to 8 weeks of use. Unfortunately, this limitation applies to both drugs."

Dr. John disclosed that he has received research support from Exact Sciences, Takeda, and Genentech, and has served as an advisor to Madrigal and Ipsen.

Credit: Adobe Stock

Mediterranean diet beats traditional dietary advice in IBS

New evidence suggests the Mediterranean diet may offer a simpler, more accessible first-line therapy for IBS, achieving superior symptom relief.

By Doug Brunk

Among individuals with irritable bowel syndrome (IBS), the Mediterranean diet proved superior to established traditional dietary advice and achieved response rates comparable to those typically expected from the low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet, according to a randomized trial.

"IBS patients rank dietary options as a top research priority, yet evidence-based choices are limited," senior author Imran Aziz, MBChB, MD, a Consultant Gastroenterologist at the University of Sheffield, United Kingdom, told *GI & Hepatology News*. "Most patients receive traditional dietary advice as first-line therapy (with only 40% responding), with non-responders escalated to the complex, restrictive low FODMAP diet requiring specialist dietetic supervision. This study addresses whether the Mediterranean diet, which is easier to implement and has established broader health benefits, could serve as an effective first-line alternative."

The study, published in the *Annals of Internal Medicine*, enrolled 139 adults across the United Kingdom who met Rome IV criteria for IBS and scored 75 or greater on the IBS Symptom Severity Scale (IBS-SSS). The researchers randomized participants 1:1 to 6 weeks of traditional dietary advice or the Mediterranean diet delivered via an online group education model, a pragmatic design reflecting real-world clinical practice. The primary endpoint was a 50-point or greater reduction on the IBS-SSS.

The researchers reported that 62% of participants assigned to the Mediterranean diet achieved the primary endpoint, compared with 42% receiving traditional dietary advice. The between-group difference favored the Mediterranean diet by 20%, demonstrating not only noninferiority but statistical superiority.

For the secondary endpoint of a 100-point or greater reduction on the IBS-SSS, response rates again numerically favored the Mediterranean die (44% vs. 32%), but this difference did not reach statistical significance. Mean improvement in IBS-SSS was significantly greater with the MD than with TDA (−101.2 vs. −64.5), with the largest separation appearing at the 6-week mark. Symptom improvements emerged early, with both groups showing significant reductions by week 2.

In other findings, both groups improved across IBS-SSS components of pain, bloating, bowel dissatisfaction, and interference with life. Only frequency of abdominal pain showed a statistically greater benefit with the Mediterranean diet. Measures of mood based on the Patient Health Questionnaire-4, somatic symptom burden based on the Patient Health Questionnaire-12, and quality of life based on the Short Form-8 Health Survey improved within groups but did not differ significantly between diets. Diet satisfaction was comparable between both groups.

The authors noted that the mechanism by which the Mediterranean diet alleviates IBS symptoms remains unclear. "Whether there is a specific or synergistic effect of the [Mediterranean diet] in beneficially regulating the microbiome–gut–brain axis warrants investigation," they wrote. "For example, the [Mediterranean diet] positively affects the gut microbiome, and some of its ingredients, such as olive oil, possess anti-inflammatory and antioxidant properties, while also reducing visceral hypersensitivity in animal models."

Dr. Aziz acknowledged certain limitations of the trial, including the inability to blind participants to their assigned diets, the 6-week duration which limits assessment of long-term benefits, and exclusion of those under 18 or over 65 years old. "The Mediterranean diet is widely available, culturally acceptable, and has numerous established health benefits," he said. "This makes it an attractive first-line option for IBS that patients can implement without requiring specialist dietetic support."

The researchers had no relevant disclosures.

Key clinical takeaways

The Mediterranean diet showed a 20% superior response rate compared to traditional advice in IBS patients.

139 adults participated in the 6-week trial based on Rome IV criteria.

Improvements in IBS symptoms were significant by week 2.

Both diets improved pain, bloating, and quality of life, but the Mediterranean diet was better for abdominal pain.

Potential mechanisms involve gut microbiome regulation.

Given its accessibility, tolerability, and established cardiometabolic benefits, the Mediterranean diet represents an attractive, evidence-based first-line dietary strategy for IBS.

Does ESD equal TAMIS for early rectal neoplasms?

"ESD was associated with fewer technical constraints, higher procedural success, shorter hospitalization, lower cost, and greater patient acceptance."

By Amy Pfeiffer

A multicenter randomized trial conducted in Spain has found that endoscopic submucosal dissection (ESD) is noninferior to transanal minimally invasive surgery (TAMIS) for the treatment of early rectal neoplasms, with comparable safety, shorter hospital stays, and substantially lower costs.

The DSETAMIS-2018 trial enrolled 73 patients with nonpedunculated early rectal neoplasms larger than 20 mm and stagedT1N0 or less. Participants were randomized to undergo either ESD (n=39) or TAMIS (n=34). The primary endpoint was 12-month local recurrence, while secondary outcomes evaluated technical success, complete (R0) and curative resection rates, procedure time, hospital stay, complications, and total cost.

At 12 months, local recurrence occurred in two patients treated with TAMIS and none treated with ESD. The absolute difference in recurrence risk was −6.7% which met the predefined noninferiority margin of 10%. Median hospital stay was one day for ESD versus two days for TAMIS, and mean procedure times were 140 minutes and 110 minutes, respectively. Both approaches demonstrated high technical success (100% for ESD vs. 89% for TAMIS) and favorable safety profiles, with similar rates of early complications, according to the results published in *Gastroenterology*.

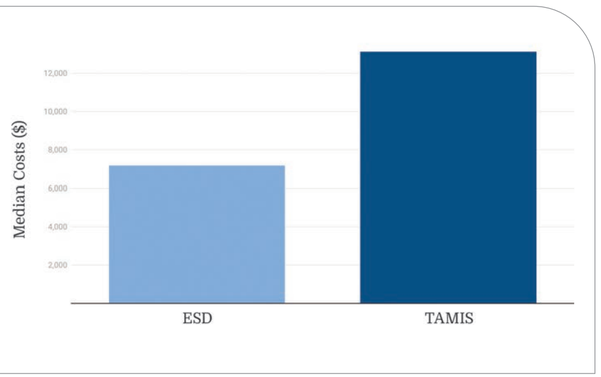
Late complications occurred in 29.6% of TAMIS cases compared with 16.3% of ESD cases, and readmission rates for late complications were higher in the TAMIS group (50%) than in the ESD group (14%). When margins were analyzed using expanded R0 criteria — accepting any tumor-free margin rather than over 1 mm — ESD achieved a complete resection rate of 93% compared with 67% for TAMIS. No cancer-related deaths were reported during a median follow-up of 15 months.

A cost analysis showed that TAMIS procedures were 83% to 103% more expensive than ESD, with median total costs of $13,135 vs. $7,175, respectively.

The findings should be interpreted with caution given the small sample size and wide noninferiority margin, noted the authors led by Diego de Frutos Rosa, MD, (Hospital Universitario Puerta de Hierro in Madrid).

Still, the investigators wrote, "ESD was associated with fewer technical constraints, higher procedural success, shorter hospitalization, lower cost, and greater patient acceptance." They emphasized that while both ESD and TAMIS remain valid options, the results support the growing role of ESD in rectal lesion management within minimally invasive oncology.

The Foundation of the Spanish Society of Gastrointestinal Endoscopy provided a fully funded research grant for the study. Investigators reported multiple disclosures.



Cost distribution: ESD $7,175, TAMIS $13,135

Jérémie Jacques, MD, a professor of gastroenterology at Limoges University Hospital, France, provided the following commentary to *GI & Hepatology News* on the implications for first-line treatment of superficial rectal neoplasia based on the study findings.

First-line management decisions

Given that ESD achieved similar oncologic outcomes with shorter hospital stays and lower overall costs than TAMIS, the implications for first-line management are substantial. The DSETAMIS randomized trial provides the first high-level, head-to-head evidence comparing ESD and TAMIS for early rectal neoplasms — and its results are difficult to overlook. When an endoscopic procedure achieves comparable oncologic efficacy, fewer complications, significantly shorter hospitalization, and dramatically lower costs, the rationale for routinely favoring a surgical approach weakens considerably.

Two additional multicenter studies — one French and one Dutch — presented at DDW 2025 and now under publication further reinforce the DSETAMIS findings. Both demonstrated similarly favorable outcomes for ESD, including significantly lower recurrence rates compared with TAMIS. When three independent cohorts across three countries converge on the same conclusion, it becomes increasingly difficult for centers to justify surgery as the default first-line option.

In Europe, this transition is already underway. Over recent years, many centers have progressively adopted ESD as the preferred first-line strategy for large superficial rectal tumors, driven by structured training programs and expanding operator experience. The DSETAMIS results therefore do not initiate this shift — they validate and accelerate a movement already in progress. These data should now encourage North American centers to follow suit, enabling patients to benefit from a minimally invasive, organ-sparing approach with proven effectiveness and substantially reduced resource utilization.

Broader eligibility for minimally invasive endoscopic treatment

The study also suggests that ESD may expand the population eligible for minimally invasive therapy. A key observation from DSETAMIS is that all crossover cases were from TAMIS to ESD, illustrating how anatomical constraints — such as proximity to the dentate line, high rectal location, or circumferential extension — may limit TAMIS feasibility but do not impede ESD.

This aligns with everyday clinical experience: a considerable proportion of rectal lesions fall outside the optimal surgical workspace yet remain entirely suitable for endoscopic resection.

When performed by operators with fully mastered expertise, rectal ESD has virtually no technical limitations, regardless of lesion size, circumferential involvement, or anatomical position — from the anal canal transition to the rectosigmoid junction — so long as indications for superficial neoplasia are respected. This represents a major distinction from TAMIS, whose safety and feasibility depend heavily on exposure, access, and working space.

Moreover, ESD has now clearly emerged as the technique of choice for all rectal polyps over 2 cm. One of the most critical and often underappreciated steps remains appropriate confirmation of indication. No superficial-appearing rectal lesion should be referred for surgery without dedicated evaluation by an ESD-trained endoscopist, ideally supported by high-quality photo documentation. This simple but essential safeguard helps prevent overtreatment and avoids unnecessary rectal surgery.

Dr. Jacques did not report having any conflicts of interest.

Histologic remission: A lifeline in IBD?

Even during clinically quiescent periods, histologic inflammation remained associated with increased mortality.

By Doug Brunk

A large national cohort study from Sweden found that both histologic inflammation and clinical activity in irritable bowel disease (IBD) are linked to higher all-cause mortality, indicating that better disease management could help lower this risk.

For the study, which was published in *Clinical Gastroenterology and Hepatology*, researchers used data in multiple Swedish national registers to compare mortality rates linked to histologic inflammation in 63,358 patients diagnosed with IBD between 1969 and 2017 and to clinical activity in 102,352 patients diagnosed between 1969 and 2020. They used a cause-specific hazard model to estimate the adjusted hazard ratio (aHR) of mortality within 2 years after index date, which was defined as the date of histologic inflammation/remission or date of clinically active/quiescent IBD.

Jiangwei Sun, PhD

"I think this work is clinically important due to two main reasons," first author Jiangwei Sun, PhD, of the Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, told *GI & Hepatology News*. "First, IBD is associated with increased mortality risk. However, whether this risk is influenced by histologic and clinical activity remains uncertain. Second, although accumulating evidence suggests that achieving histologic remission is associated with improved clinical outcomes, the potential value of histologic remission on reducing death risk remains unknown. We found increased absolute and relative rate of 2-year mortality associated with histologic inflammation."

Across more than 155,000 histologic periods, the 2-year all-cause mortality rate was 121 per 10,000 person-years following histologic inflammation, compared with 64.8 following histologic remission. The adjusted hazard ratio told the story clearly: a 45% increased mortality risk after histologic inflammation. And this wasn't confined to ulcerative colitis. The excess extended to Crohn's disease (aHR 1.42) and IBD-unclassified (aHR 1.56), signaling that the prognostic value of histologic remission transcended disease subtype.

The cause-specific mortality patterns deepened the concern. Histologic inflammation carried elevated risks of death from cardiovascular diseases (aHR 1.48), malignant neoplasms (aHR 1.26), and digestive diseases (aHR 2.29). In patients with UC, deaths from infectious disease were also increased. Even in sensitivity analyses — shortening the presumed duration of histologic inflammation to 6 months or extending the follow-up to 5 years — the signal persisted.

Yet one finding surprised the researchers: even during clinically quiescent periods, histologic inflammation remained associated with increased mortality (aHR 1.42). "Our study is the first to show that, even without proxies for clinical activity, histologic inflammation was associated with a 42% increased risk of death, suggesting the potential value of achieving histologic remission in clinical practice," Sun said.

He acknowledged certain limitations of the study, including the potential for misclassification of histologic and clinical activity. "Our definition of histology activity was not based on a histologic scoring system such as the Nancy Histological Index and lacked information on inflammation severity or its cumulative impact over time," Sun explained. "Moreover, we lacked data on indications for histologic assessment (e.g., determining disease severity or estimating the efficacy of treatment), endoscopic quality, macroscopic appearance, and inflammatory markers for define disease activity."

Sun added that, because data on the dose and frequency of targeted therapies were unavailable, their measure of clinical activity relied solely on health administrative records and was driven largely by corticosteroid use. As a result, their analysis may have predominantly captured patients with moderate-to-severe disease activity.

"Furthermore, we must acknowledge that our definition for clinically quiescent IBD may still include patients with clinical or endoscopic activity (e.g., using 5-aminosalicylic acid therapy)," he said. "More studies are warranted to validate our definitions of histologic and clinical activities and our findings."

The study was supported by the Swedish Society for Medical Research, the European Crohn's and Colitis Organization, the Swedish Society of Medicine, the Ruth and Richard Julin Foundation, and the Karolinska Institute.

Sun reported having no disclosures.

CRC screening: Smartphone-based stool test matches lab accuracy

New findings point to a tool for enhancing participation in CRC screening programs — particularly among younger, tech-savvy patients under 60 years who demonstrate higher adoption rates.

By Amy Pfeiffer

A smartphone-based fecal immunochemical test (FIT) was found to be a reliable and accessible tool for colorectal cancer (CRC) screening, according to the results of a new population-based study published in *Clinical Gastroenterology and Hepatology*. The mobile app–enabled FIT achieved diagnostic performance comparable to laboratory-based FITs while significantly improving patient convenience and participation.

"In this first study to evaluate the utilization and performance of a digital smartphone-based test for early detection of CRC at home, more than one-half of the participants made use of the test, with higher rates among male participants and the most important target group under age 60 years," reported Michael Hoffmeister, PhD, of the German Cancer Research Center in Heidelberg, and colleagues.

The researchers enrolled 654 patients who were scheduled for screening colonoscopy across gastroenterology practices in southern Germany between 2021 and 2023. Participants were offered both a smartphone-based FIT (SmarTest FIT) and a laboratory-based FIT (FOB Gold). Fifty-five percent of participants used the smartphone-based FIT, while 98% used the laboratory FIT. Of those who used the smartphone test, 76% had valid results. Overall, 89% of participants found the smartphone-based FIT a useful alternative to the standard test.

Of the 361 participants using the smartphone-based FIT, 24% (87 people) had a failed test — meaning they began the process but did not submit a result. Among those with failed tests, 32% did not own a smartphone, and 51% encountered issues during testing — most often believing they had completed it (34%).

The sensitivity for detecting advanced neoplasms was 28% for the smartphone-based FIT vs 34% for the laboratory FIT, with identical specificity at 92%. Receiver operating characteristic analysis showed nearly equivalent — though not statistically significant — diagnostic accuracy, which suggested that the smartphone-based approach performs on par with standard FITs under real-world conditions.

The smartphone-based FIT uses a rapid immunochemical test cassette that is analyzed through a smartphone app and quantifies hemoglobin concentration in stool via color intensity. Users collect a stool sample, apply it to the cassette, and scan the test after 15 minutes using their phone's camera, reported Hoffmeister and colleagues.

A feasibility questionnaire revealed overwhelmingly positive patient feedback. Of the participants, 92% agreed the app offered clear guidance, 94% found stool handling manageable, 89% felt test duration was appropriate, and 78% supported immediate result display within the app. Common barriers among nonusers included technical issues (47%), such as app or smartphone compatibility, and general skepticism toward digital testing (44%).

The findings point to a new tool for enhancing participation in CRC screening programs — particularly among younger, tech-savvy patients under 60 years who demonstrated higher adoption rates, noted investigators. Although colonoscopy remains the diagnostic gold standard, smartphone-based FITs could bridge gaps in accessibility by enabling at-home testing and digital result transmission. A positive test result, however, must still be followed by colonoscopy and physician consultation, they emphasized.

Integrating digital self-tests could help increase participation rates in colorectal cancer screening overall, provided quality controls are maintained. Further research may focus on long-term adherence, impact on CRC detection rates, and cost-effectiveness within organized screening programs.

The researchers disclosed no conflicts of interest.

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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/mm³). Treatment with RINVOQ is not recommended in patients with an ANC <1000 cells/mm³. Evaluate neutrophil counts at baseline and thereafter according to routine patient management.

Lymphopenia

Absolute lymphocyte counts (ALC) <500 cells/mm³ were reported in RINVOQ-treated patients. Treatment with RINVOQ is not recommended in patients with an ALC <500 cells/mm³. 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.

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/mm³).

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/mm³).

Lymphopenia

ALC less than 500 cells/mm³ 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/mm³).

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	RINVOQ 15 mg
	N = 1042 (%)	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 (8.4 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 spondyloarthritis, 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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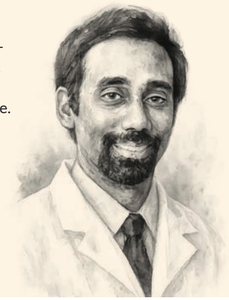
GI experts debate ESG, GLP-1 roles in modern obesity treatment strategies

Dear colleagues,

Two years ago, we asked whether gastroenterologists were ready to take the lead in managing obesity. Since then, the landscape has shifted dramatically. Landmark pharmacologic advances — particularly GLP-1 receptor agonists — have become household names, and the conversation around weight loss now permeates nearly every corner of medicine. But with broader adoption comes new questions: Should we favor medications over procedures? How durable are these interventions? Can endoscopic sleeve gastroplasty (ESG) and pharmacotherapy work together? And where do we, as gastroenterologists, fit in?

In this issue, Dr. Marianna Papademetriou makes a strong case for embracing medical weight loss tools — including GLP-1 RAs — as a natural extension of practice, grounded in physiology, patient need, and existing expertise. Drs. Eric Vargas and Dan Maselli counter with an equally compelling defense of ESG, arguing that endobariatrics remains a vital, underused tool — and that it's time for greater integration, not replacement.

As this field continues to evolve, these commentaries remind us that effective weight loss care requires a multidisciplinary, patient-centered approach, using an ever-growing armamentarium of endoscopic and pharmacologic treatments. We hope these perspectives help guide how you approach weight loss management in your own practice.



Gyanprakash A. Ketwaroo, MD, MSc, is associate professor of medicine, Yale University, New Haven, and chief of endoscopy at West Haven VA Medical Center, both in Connecticut. He is an associate editor for GI & Hepatology News.

All of your patients are already on GLP-1s

By Marianna Papademetriou, MD

In our medical careers, the approval and widespread uptake of incretin mimetics, more commonly GLP-1RAs, represent a turning point in obesity management. Historically, the management of obesity relied on lifestyle modifications and limited pharmacologic options, both of which offered modest results and were difficult to sustain long term. Now, with the advent of GLP-1RAs — recently FDA-approved for obesity, metabolic associated steatohepatitis (MASH), cardiac disease, and sleep apnea — has fundamentally altered this paradigm. Gastroenterologists are uniquely positioned to lead the integration of GLP-1 therapies into our established practices.

We have had safe, effective, and durable treatment through bariatric and metabolic surgery for decades. In the last 10 years, endoscopic bariatric and metabolic procedures (EBMTs) have also been developed and evolved to include a variety of options to tailor to individual patient goals and needs.[1] However, uptake of surgical procedures has stagnated at around 270,000 per year, representing a fraction of eligible US patients.[2]

EBMTs likewise, are still limited geographically and have not historically been covered by commercial insurance, although we are on the verge of this changing with the new CPT codes in 2026. Notably, because we know obesity is chronic, relapsing, and significantly under-treated, there is clearly need for an all-hands-on-deck approach with available modalities.

I'll discuss three main reasons why gastroenterologists are already ideally positioned to prescribe and support the use of GLP1-RA as part of this evolving landscape. First, many patients are already on GLP1s, with or without the support of clinicians with expertise in this field and may be better served with thoughtful clinician guidance. Additionally, many GI conditions can improve with the significant weight loss achieved on GLP1RA. Third, the most common side effects are GI related; and, therefore, gastroenterologists are primed to help with management and personalization.

Widespread patient adoption of GLP-1RAs

A recent Kaiser Family Foundation poll found that one in five US adults report ever being on a GLP1-RA.[3] In 2024, when both semaglutide and tirzepatide were on the national drug shortage list, a large compounding industry developed to fill the gap. Access barriers, from cost to health-care bias, were removed as patients could order medications from the comfort of their homes. Reddit and Facebook support groups appeared for patients to counsel each other.

Many were successful in reaching their weight-loss goals. However, with time we've accumulated more experience for optimizing care. Patients may benefit even further from gastroenterologist guidance through the process to help counter lean muscle mass and bone loss, avoid nutritional deficiencies, and titrate medications for comorbidities.[4]

Expanding clinical indications

GLP1-RAs are now approved for more indications beyond treatment of overweight and obesity. Semaglutide was recently approved for metabolic associated steatohepatitis (MASH). Tirzepatide is approved for the treatment of sleep apnea. While not approved specifically for these conditions, obesity is an independent risk factor for the development of many GI cancers.

Well known profile of side effects

Rather infamously, GLP1-RAs are associated with a variety of side effects. Curiously, I have never encountered a class of medications where patients are more willing to tolerate said side effects and persevere than when prescribing GLP1-RAs. Dose escalation to levels where significant weight loss is achieved also includes a transitional period where patients may experience nausea, vomiting, reflux, dyspepsia, diarrhea, or constipation. Gallstones and biliary disease are also seen. Some patients require longer lead in periods before doses are escalated.

GLP1-RAs are here to stay. As the therapeutic landscape continues to evolve, it is incumbent upon gastroenterologists to embrace evidence-based use of GLP-1RAs, coordinate multidisciplinary care to maximize patient outcomes, and optimize management of adverse effects. Future research is needed to best customize long-term therapy for efficient weight maintenance and cost-effectiveness.

Dr. Papademetriou is an assistant professor at the VA Medical Center in Washington, DC.

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ESG: An effective complement to the pharmacologic era

By Eric Vargas, MD, and Dan Maselli, MD

The evolving role of ESG

Over the past decade, ESG has matured from an innovative concept into a safe, reproducible, and durable intervention for weight loss. Initially introduced as a minimally invasive alternative to surgical sleeve gastrectomy, ESG has steadily refined its technique, safety, and outcomes. Today, it occupies a unique position within the continuum of obesity care, bridging the gap between lifestyle interventions, pharmacotherapy, and surgery.

As obesity care enters a robust pharmacologic era defined by increasingly potent gut-hormone agonists, ESG offers versatility as a durable anatomical therapy for a variety of patients: those seeking alternatives to long-term medications, those seeing weight return after medication cessation, and those aiming for surgical-level health benefits through complementary therapy that combines ESG with medications. This reflects a broader shift toward flexible, patient-centered strategies that address the chronic and multifactorial nature of obesity.

Incretin-mimetic revolution

GLP-1 receptor agonists and other incretin mimetics has transformed the obesity landscape. Their efficacy has enabled many patients to achieve meaningful weight loss, often for the first time in their lives, and has dramatically increased public awareness on obesity as a treatable condition.

However, real-world practice has revealed a predictable challenge: weight recurrence when medications are reduced or discontinued. Interruptions due to cost, insurance variability, supply shortages, intolerable side effects, pregnancy planning, or patient preference frequently trigger weight regain. Across the endobariatrics landscape, we increasingly encounter patients who achieved substantial weight loss from medications but now seek a durable solution as they reconsider, taper, or discontinue lifelong pharmacotherapy. For many, losing progress after investing deeply in their weight loss-journey can be profoundly discouraging.

ESG as a stabilizing partner

Here is where ESG demonstrates its greatest value in the pharmacologic era of obesity management. Unlike medications that rely on continuous use, ESG provides a durable anatomical change that reinforces satiety, reduces gastric volume, and supports long-term behavior modification. The literature and clinical experience repeatedly show adherence to GLP-1 based medications does not extend beyond one to two years for the majority of patients with obesity. As leaders of the Metabolic & Bariatric Endoscopy Program at Mayo Clinic Rochester, we have seen firsthand how ESG mitigates the rebound that consistently follows pharmacotherapy tapering. Patients who undergo ESG while on GLP-1 therapy, and later reduce or discontinue medication, experience far more stable long-term weight trajectories compared with those who taper medications alone.

The combination is synergistic: pharmacotherapy initiates weight loss, and ESG anchors it. This partnership improves outcomes, reinforces adherence, and reduces the anxiety many patients feel about stopping obesity medications.

Looking ahead: The multi-agonist era

The next generation of pharmacologic agents promises even greater efficacy. Retatrutide, a triple GIP/GLP-1/glucagon agonist, has demonstrated early results approaching surgical-level weight loss. These developments are remarkable and welcomed. Yet all gut-hormone agonists share core limitations: they require ongoing use, tolerability varies, costs and coverage remain uncertain, discontinuation consistently leads to weight and comorbidity recurrence.

These emerging therapies will only increase the relevance of ESG. As medications become more potent, the need for a stabilizing anatomical intervention that sustains weight loss beyond active pharmacotherapy will grow. ESG provides the foundation, functioning as a minimally invasive, long-term anchor in a multimodal treatment strategy.

Flexibility and surgical compatibility

A key advantage of ESG is its versatility. Although typically performed once, ESG can be safely repeated in patients with gastric dilation or partial weight recurrence — findings consistent with obesity as a chronic, relapsing disease with multiple redundant pathways. In our practice, reinforcing a previously placed sleeve has restored physiologic benefit in selected patients, a capability unique among minimally invasive interventions.

ESG also integrates well with bariatric surgery. It can be performed after removal of an adjustable gastric band or to revise a dilated surgical sleeve. Conversely, ESG can enhance pre-operative feasibility in patients with high BMI, significant metabolic disease, or inadequate response to medications who are preparing for bariatric surgery. Patients who undergo ESG before surgery often find the eventual transition to surgery both physically and psychologically easier. For many, progressing from medication to ESG to surgery feels more intuitive than moving directly from medication to a surgical intervention.

Durability, metabolic effects, and endorsement

Long-term data further validate ESG's role in comprehensive obesity management. Five-year studies now demonstrate sustained 10-15% total body weight loss, low rates of adverse events(<1%), and durable improvements in comorbid conditions such as type 2 diabetes, MASLD, and cardiovascular disease. These findings align with the IFSO Bariatric Endoscopy Committee's recent evidence-based review endorsing ESG as a validated, durable, and integral therapy.

Expanding access and infrastructure

ESG's utility is further strengthened by emerging policy and infrastructure. A dedicated Category I CPT code for ESG will take effect in January 2026, reflecting mainstream recognition of the procedure as an evidence-based therapy. Several private insurers have already added ESG as a covered benefit, including Mayo Clinic, expanding access and helping narrow equity gaps for patients who may not have the means or desire to remain on lifelong pharmacotherapy.

Within our program, we have observed how coordinated follow-up, multidisciplinary care, and structured training platforms create sustainable ESG practices. These elements will be essential to scaling ESG responsibly across diverse clinical settings.

ESG and the future of metabolic endoscopy

More than a decade into its use, ESG has clearly proven the value of endoscopic gastric remodeling for patients with obesity and related metabolic disease. Yet this is only the beginning. As ESG is increasingly paired with incretin-based medications to achieve weight-loss outcomes approaching bariatric surgery, its role as a platform for combination metabolic endoscopic therapies is becoming clear. Emerging approaches — including gastric fundal mucosal ablation to reduce ghrelin and duodenal mucosal ablation to improve insulin resistance — offer new, targeted ways to modulate appetite and metabolism. Together, these mucosal interventions and ESG could evolve into a single-stage, incisionless combination procedure delivered safely in the ambulatory setting at experienced endobariatric centers.

Conclusion

After following patients for many years, it is clear that ESG offers durability, flexibility, and compatibility with both pharmacotherapy and surgery — attributes increasingly important in a landscape shaped by potent incretin-based and multi-agonist medications. For some patients, ESG will serve as a meaningful alternative to medications; for many others, it will enhance and stabilize pharmacotherapy-induced weight loss. As access expands, ESG will remain a central tool for long-term, sustainable obesity management in the pharmacologic era.

Dr. Vargas is an interventional endoscopist and assistant professor of medicine at Mayo Clinic Rochester. Dr. Maselli is a gastroenterologist in Atlanta, GA, practicing at True You Weight Loss.

Dr. Vargas disclosed that he has received research support from Boston Scientific and Phillips Healthcare. Dr. Maselli disclosed that he has conducted prior consulting for Apollo Endosurgery/Boston Scientific.

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Sarcopenia, thrombosis, and renal dysfunction dominate cirrhosis complication updates

New diagnostic approaches and treatment controversies emerge for managing advanced liver disease.

By Kerri Miller

Updated guidance on three major complications affecting patients with cirrhosis — sarcopenia management in hepatic disorders, portal vein thrombosis treatment stratification, and hepatorenal syndrome therapeutic approaches — were presented at the United European Gastroenterology Week in Berlin in a joint session.

Sarcopenia: beyond muscle mass quantification

Francesca Ponziani, MD, from Fondazione Policlinico Universitario Agostino Gemelli IRCCS in Rome, noted that sarcopenia affects approximately 40% of patients with cirrhosis and represents a diagnosis requiring reassessment at each patient evaluation. The condition is defined by three criteria: loss of muscle strength, compromised muscle quantity or quality, and impaired physical performance.

Dr. Ponziani distinguished between frailty and sarcopenia, noting that "frailty is the phenotypic representation of an impaired muscle contracting function, and sarcopenia is instead referred to mainly to the loss of muscle mass." She recommended the liver frailty index — comprising handgrip strength, chair stance, and balance exercise — as the most practical clinical tool. "Frailty testing can be used in everyday clinical practice to suspect the sarcopenia and loss of muscle function and sarcopenia. Testing and quantification may be reserved for those patients that cannot be addressed by this kind of testing," she said.

The mechanisms driving sarcopenia in cirrhosis differ substantially from those in without cirrhosis. Dr. Ponziani presented data linking ammonia production to myostatin upregulation through inflammatory pathways (specifically mentioning protein p65 expression), with research showing myostatin as "a good predictor of sarcopenia" that can be used clinically when possible, she noted.

Gut microbiota dysbiosis emerged as a significant contributor. Mouse model studies demonstrated that rifaximin administration reduced myostatin levels and expression while increasing muscle mass. Dr. Ponziani's group identified reduced alpha diversity characterizing gut microbiota in patients with sarcopenia and cirrhosis, with markers of dysbiosis including increased Klebsiella, altered metabolism of nitrogen and branched amino acids, and endogenous ethanol production. Additional research showed that Ruminococcaceae depletion was associated with amino acid metabolism alterations and increased risk of sarcopenia and cirrhosis complications.

Treatment centers on three prevention levels: primary prevention to delay onset, secondary prevention with dietitian co-management and certified physical therapy, and tertiary prevention utilizing center-based rehabilitation.

Dr. Ponziani noted that testosterone treatment demonstrated muscle mass reversal in limited studies, with one 2025 simulation study suggesting mortality benefits, though she noted: "We don't know the extent we can reverse this kind of alteration."

Portal vein thrombosis: etiology determines management

Verena Keitel-Anselmino, MD, from University Hospital, Magdeburg in Germany, presented contrasting approaches for cirrhotic versus non-cirrhotic portal vein thrombosis (PVT).

The prevalence in cirrhosis reaches 14% overall, with annual incidence ranging from 4.6% to 26%, increasing with cirrhosis severity and portal hypertension. Hepatocellular carcinoma represents an independent risk factor, with 1-year incidence reaching 25%, and 50% of PVT cases diagnosed when patients are listed for transplantation.

Risk factors in cirrhosis differ fundamentally from non-cirrhotic disease. "The risk factors you find in liver disease are all related to portal hypertension," said Dr. Keitel-Anselmino. A prospective French study identified reduced portal vein blood flow (hazard ratio 3), previous variceal bleeding, low platelets, and large spleen as key risk factors, with coagulation factors showing minimal association.

PVT complications include worsened variceal bleeding with increased 5-day treatment failure and 6-week mortality, portal cholangiopathy, mesenteric ischemia with high mortality, and complicated liver transplantation. However, "if you don't look at a variceal bleed, there is no association with prognosis and long term cirrhosis outcome," noted Dr. Keitel-Anselmino.

A recent meta-analysis demonstrated anticoagulation reduces all-cause mortality independent of PVT severity, with significantly higher recanalization rates and stable thrombus in non-treated patients. Critically, bleeding occurrence was identical between treatment groups. "Anticoagulation does have an effect besides the recanalization of the portal vein," said Dr. Keitel-Anselmino.

Treatment recommendations specify low molecular weight heparin or direct oral anticoagulants (DOACs), with DOACs showing fewer bleeding events than vitamin K antagonists in meta-analyses. "Proceed with caution in Child B and be very restrictive in Child C" for DOAC use, advised Dr. Keitel-Anselmino. Treatment duration targets recanalization (minimum 6 months) or indefinite treatment for transplant candidates.

For refractory cases, transjugular intrahepatic portosystemic shunt (TIPS) achieves above 90% technical success and complete recanalization, even with cavernous transformation. A case series showed 67% of thrombotic patients underwent TIPS through splenic access with high success rates and similar complication rates to standard approaches.

Hepatorenal syndrome: inflammation challenges functional model

Raj Mookerjee, MD, from University College London, challenged the purely functional conceptualization of hepatorenal syndrome (HRS), presenting evidence for structural kidney damage and inflammation's role in pathophysiology and treatment response.

The acute kidney injury (AKI) staging system now incorporates urine output alongside creatinine changes, addressing sarcopenia's confounding effect on creatinine values in patients with cirrhosis. Stage 1 AKI (creatinine below 135 µmol/L or 1.5 mg/dL) patients demonstrate twice the survival of those with advanced stages.

Dr. Mookerjee presented kidney biopsy data showing toll-like receptor 4 staining in tubules of patients labeled with functional renal failure, though less than those with documented tubular injury. "If we look at inflammation, and we look at the role here of urine marker expression, one sees much worse outcome in those patients that are positive," he said.

Testosterone treatment demonstrated muscle mass reversal in limited studies for sarcopenia, with one simulation suggesting mortality benefits.
- Francesca Ponziani, MD

Dr. Francesca Ponziani

Dr. Verena Keitel-Anselmino

Dr. Raj Mookerjee

Renal histology from so-called functional HRS patients revealed renal vascular injury elements and both tubular and glomerular injury. "Highlighting the functional is a label that we've applied as clinicians. But there are still structural elements to address," said Dr. Mookerjee.

Systemic inflammatory response syndrome criteria correlated with outcome regardless of infection resolution in a study segregating HRS patients by infection status. "Those who actually had a marked increase inflammatory response had poor outcome," suggesting inflammation impacts physiology and treatment response beyond reversible vasomotor elements, noted Dr. Mookerjee.

For treatment, he outlined a systematic approach: remove nephrotoxic factors (including aminoglycosides, NSAIDs, beta-blockers in advanced cases), provide volume replacement with albumin for non-colloidal properties, then initiate vasoconstrictors if AKI criteria persist after 48 hours.

Terlipressin with albumin remains the European standard, preferably administered as continuous infusion starting at 2 mg daily, increasing to maximum 12 mg daily. The CONFIRM trial demonstrated terlipressin superiority over albumin alone for reversing HRS and reducing renal replacement therapy requirements, though 90-day survival benefits did not persist.

Subanalysis revealed patients with higher acute-on-chronic liver failure (ACLF) grades, particularly grade 3, experienced significantly more respiratory failure. "There's something in the biology of evolution of that inflammatory response that makes capillaries perhaps more leaky in the context of the lung, but also much worse in terms of the overall systemic hemodynamics," explained Mookerjee.

Terlipressin reduces cardiac output by at least 15% in treated patients, as demonstrated by phase-contrast MRI studies. "In patients who've got more advanced disease, is perhaps taking that important kick that's needed from the compensation of cardiac output away," he said. Monitoring mean arterial pressure, noting lack of sustained increase above 5 mmHg may indicate poor response.

Alternative vasoconstrictors include midodrine with octreotide (lower response than terlipressin) and noradrenaline (requiring ICU setting). TIPS remains under investigation for HRS, with the ongoing Liver Hero trial results pending.

Urinary neutrophil gelatinase-associated lipocalin emerged as a prognostic marker, with lower levels predicting better response to terlipressin-albumin therapy. "We don't have many histological correlates with this," he noted, however.

Approximately 50% of discharged AKI patients require readmission within three months for renal or metabolic complications, with higher chronic kidney disease progression risk. "I think we do need much better stratification of patients using validated markers that will help us improve outcomes in therapy," concluded Dr. Mookerjee.

Evaluating the benefit-risk profile of upadacitinib in IBD

Across multiple IBD trials, "upadacitinib consistently outperforms placebo with a generally favorable safety profile across diverse patient subgroups."

By Doug Brunk

Across phase 2b/3 trials of patients with Crohn's disease and ulcerative colitis, the oral, reversible Janus kinase inhibitor (JAK) upadacitinib consistently outperformed placebo in induction and maintenance, regardless of cardiovascular risk, age, or treatment history, a post hoc analysis showed. Improvements were seen in clinical remission, endoscopic outcomes, symptom scores, and patient-reported outcomes.

"Our findings suggest the favorable benefit-risk profile of upadacitinib for the treatment of moderately to severely active Crohn's disease and ulcerative colitis in general, and for the specific subgroups evaluated," corresponding author Edward Loftus, Jr., MD, of the Mayo Clinic, Rochester, Minnesota, and colleagues wrote.

The findings come from a pooled analysis of phase 2b/3 induction and maintenance trials in Crohn's disease and ulcerative colitis. Induction used upadacitinib 45 mg daily for 8 weeks (ulcerative colitis) or 12 weeks (Crohn's disease), with induction responders re-randomized to upadacitinib 15 mg, upadacitinib 30 mg, or placebo for 52-week maintenance, according to the analysis published in the Journal of Crohn's and Colitis.

The analysis looked at 1,021 patients with Crohn's disease and 1,097 with ulcerative colitis during the induction phase, and 673 patients with Crohn's disease and 746 with ulcerative colitis during maintenance.

Upadacitinib 30 mg showed numerically higher efficacy than 15 mg in nearly every subgroup examined. This pattern was observed in Crohn's disease (AI remission, endoscopic endpoints) and ulcerative colitis (clinical and endoscopic remission, maintenance of response). This reinforces the practical approach of reserving 30 mg for patients requiring sustained, deeper disease control, especially younger patients or those with prior biologic failure, noted investigators.

In terms of safety, across subgroups, rates of major adverse cardiovascular events (MACE), venous thromboembolism (VTE), malignancy (excluding non-melanoma skin cancer [NMSC]), NMSC, and gastrointestinal perforation were low and comparable between upadacitinib and placebo during both the induction and maintenance phases. The authors noted that this is clinically important given concerns about JAK inhibitor safety derived from rheumatoid arthritis. The IBD population in this analysis, which was generally younger and with different comorbidity profiles, showed no signal for increased MACE or VTE risk.

Herpes zoster incidence was higher with upadacitinib across most subgroups, especially with the 30 mg dose and in Crohn's disease. This pattern was consistent across cardiovascular risk categories, biologic-experience subgroups, and younger age groups (<50 years) in Crohn's disease. Ulcerative colitis showed similar trends, though the magnitude was somewhat lower.

Considering the low baseline zoster vaccination rates in the study population, the findings reinforce existing practice guidelines that zoster vaccination should be strongly considered before initiating upadacitinib.

A modest numerical increase in serious infections was observed with upadacitinib 30 mg versus placebo during Crohn's disease maintenance, particularly in patients without an inadequate response to biologic therapy, though absolute rates remained low. This pattern was not seen in ulcerative colitis to the same extent. Clinically, the authors noted, this supports vigilance in patients with additional infection risk factors, particularly when using the higher maintenance dose. The authors acknowledged certain limitations of their analysis, including the lack of predefined endpoints and small patient numbers in the subgroups. "The results should be considered exploratory, warranting further research," they wrote.

Cuckoo Choudhary, MD, a spokesperson for AGA and professor of medicine at Thomas Jefferson University, Philadelphia, who was not involved with the study, said that the post hoc analysis provides several actionable conclusions:

- Upadacitinib demonstrates consistent efficacy across key patient subgroups, "supporting its use regardless of cardiovascular risk, age, or prior biologic exposure," she said.

- Upadacitinib 30 mg delivers the strongest maintenance efficacy, "appropriate for patients with more refractory or aggressive disease."

- Safety signals observed in RA populations were not reproduced in IBD, "except for expected increases in herpes zoster and mild increases in serious infections (mainly Crohn's disease, upadacitinib 30 mg)."

- Zoster vaccination should be prioritized, "particularly in younger patients and those starting 30 mg," she added.

- For patients aged 65 and older, data is reassuring but limited. "Individualized decision-making and shared discussion of uncertainties remain important," she said.

Across multiple IBD trials, "upadacitinib consistently outperforms placebo with a generally favorable safety profile across diverse patient subgroups. These findings support its role as a flexible, potent therapeutic option," noted Choudhary.

The study was supported by AbbVie, which designed the trials. Dr. Loftus disclosed that he has served as a consultant for AbbVie and for several other pharmaceutical companies. He also holds shares in Exact Sciences and Moderna. Dr. Choudhary reported having no disclosures.

Dr. Loftus discussed study highlights in an interview with *GI & Hepatology News*.

What is the main clinical take-home message of this trial?

Dr. Loftus: The results overall are reassuring and overall, the benefit-risk profile for most IBD patients is favorable. However, it is important to recommend zoster vaccination in patients who have started or are about to start upadacitinib.

When you had all the data in front of you, was there a finding, or perhaps more than one, that surprised you?

Dr. Loftus: I was somewhat surprised to see that there was no elevated signal for MACE even in the high cardiovascular risk subgroup. This was defined by age, smoking (current or within 15 years) obesity, cardiovascular history, diabetes mellitus, hypertension, thromboembolism, etc.

Why is this research important? What gap(s) in knowledge or therapeutics does it seek to fill?

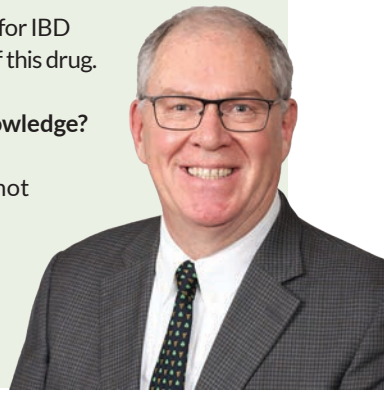
Dr. Loftus: We often talk about the efficacy and safety of new therapies in isolation. Upadacitinib is highly potent and fast acting in IBD, but the label carries boxed warnings. In this post hoc analysis of over 2,000 IBD patients in pivotal trials of upadacitinib, we looked at the efficacy and safety of upadacitinib side by side in subgroups of interest, including in those with either low or high cardiovascular risk, those with either prior biologic treatment failure (including anti-TNF specifically) or not, and in age subgroups. The efficacy of upadacitinib was higher than placebo in all of the subgroups, and safety wise the subgroups were comparable between upadacitinib and placebo except for a signal for herpes zoster in Crohn's patients on upadacitinib and a nonsignificant higher rate of serious infections in Crohn's patients on upadacitinib.

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

Dr. Loftus: Longer follow-up of patients on upadacitinib for IBD will help answer questions about the long-term safety of this drug.

Are there limitations to the study you'd like to acknowledge?

Dr. Loftus: First of all, this was a post hoc analysis, not prespecified. Although there were over 2,000 patients in this analysis, it still might not be big enough to detect small differences in safety outcomes especially for less frequent events.



Dr. Richa Shukla blends IBD expertise, mentorship, and women's health advocacy

From fellowship training to national leadership, she's redefining what it means to care, teach, and advocate.

By Sierra Rendon

A driving force in modern inflammatory bowel disease (IBD) care and medical education, Richa Shukla, MD, is an associate professor in Gastroenterology and Hepatology at Baylor College of Medicine (BCM), recognized for her leadership and dedication to trainees. Her career began with an internal medicine residency at Mount Sinai Hospital in New York City, followed by general GI and advanced IBD fellowship training at BCM — experiences that solidified her expertise in complex IBD and her commitment to long-term patient care.

As associate program director of the GI Fellowship at BCM, she guides trainees in shaping their goals and navigating early academic careers, complemented by national service on the AGA Education and Training Committee and the AGA Academy of Educators. Dr. Shukla is also a strong advocate for women's health in IBD and for policies supporting women in gastroenterology. Balancing her roles as clinician, educator, and mother of three, she leads with authenticity and resilience. In a recent interview, she reflected on the motivations and values that have shaped her journey.

What drew you to focus on IBD as your subspecialty within gastroenterology?

Dr. Shukla: I have always valued creating long-term, meaningful relationships with my patients. I find that IBD lends itself to this. Getting to know my patients beyond their disease is one of the most rewarding aspects of this job. Furthermore, I love the cerebral nature of IBD and enjoy the feeling of constantly being challenged by complex patients. I am often humbled by new presentations of a disease I have been managing for years. I credit my friend and colleague, Manreet Kaur, MD, with inspiring me to pursue a career in IBD.

As a leader in medical education, what do you find most rewarding about training the next generation of gastroenterologists?

Dr. Shukla: I can still recall my own experiences in training and what a profound impact a good mentor made. Being involved in medical education is my way of trying to pay it forward. I believe that I can help fellows by sharing my own successes and pitfalls and use these lessons to help fellows achieve what they envision for their future careers.

You've completed advanced fellowship training in IBD — how has this shaped your approach, especially in complex cases?

Dr. Shukla: While an advanced year is by no means a requirement to care for complex IBD patients, it made a world of a difference for me to gain the confidence I needed. Furthermore, it taught me the skills to troubleshoot any unusual presentations of IBD. Through this experience, I feel that I am better prepared to also guide fellows through the challenges that can sometimes make IBD feel intimidating. I am very excited about possible new mechanisms of action in the treatment pipeline and, perhaps even more impactful, the role of personalized medicine.

Women's health is another area of your professional interest. How do you incorporate this into your IBD practice, especially when treating young women of childbearing age?

Dr. Shukla: I believe women often seek out other women for their medical needs, especially when it involves something that can be somewhat personal and sensitive like gut health. I think it is of utmost importance to be prepared for the type of questions on women's minds and with the younger age of most IBD patients, pregnancy related questions come up quite often. I try to proactively address what types of questions and concerns could be relevant to a woman of childbearing age and ensure my knowledge is always up to date.

The Crohn's & Colitis Congress® is just around the corner — what sessions or topics are you most looking forward to this year?

Dr. Shukla: The Crohn's & Colitis Congress is an excellent, cutting-edge meeting where you can really get the latest and greatest in the world of IBD. I hope to see more data on the novel mechanism of action of TL1A and its impact on the goal of achieving higher rates of remission in our patient population. I also would like to see more data on how to use combination advanced therapy in managing our most refractory patients. If you're a first-time attendee I recommend attending the IBD A–Z sessions.

You wear many hats! What does a typical day look like for you, and how do you find balance?

Dr. Shukla: I've heard this advice many times, and it really resonates with me, which is why I think this is a great platform to share it. I don't believe anyone can truly achieve perfect balance — which implies an equal division of time and energy across all commitments. Instead, I've learned that at any given moment, one priority may take "center stage" and demand more focus, and that's okay.

What advice would you give to early-career physicians — especially women — considering a career in academic medicine or IBD?

Dr. Shukla: As a woman in the early-career setting, we sometimes have to make decisions that allow for the best fit among our competing priorities. As life evolves and those priorities shift, it's important to continue loving the work you do. With that in mind, I've found academic medicine — and IBD in particular — to be both deeply rewarding and conducive to a strong work–life balance, allowing me the time I want and need with my family.

What's something your colleagues might be surprised to learn about you outside of work?

Dr. Shukla: While being a Houston sports fan is often a losing cause, I am still a big fan of the Texans, Rockets, and Astros. I've leveraged my interest in football into a success career as a fantasy football team manager, and I won my league's championship last year!

Lightning round

What's your secret talent?

My friends call me a human IMDb. I am a big movie buff and know the ins and outs of the cast and more on-demand!

Sweet or savory?

Sweet.

If you could instantly learn any skill, what would it be?

Sewing.

What would you be if you weren't a GI?

I'd love to have Rick Steves' job.

What's your favorite comfort food?

Chocolate-chip cookies.

Would you rather read the book or watch the movie?

Read the book, 1,000/1,000 times.

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