

GI & Hepatology News

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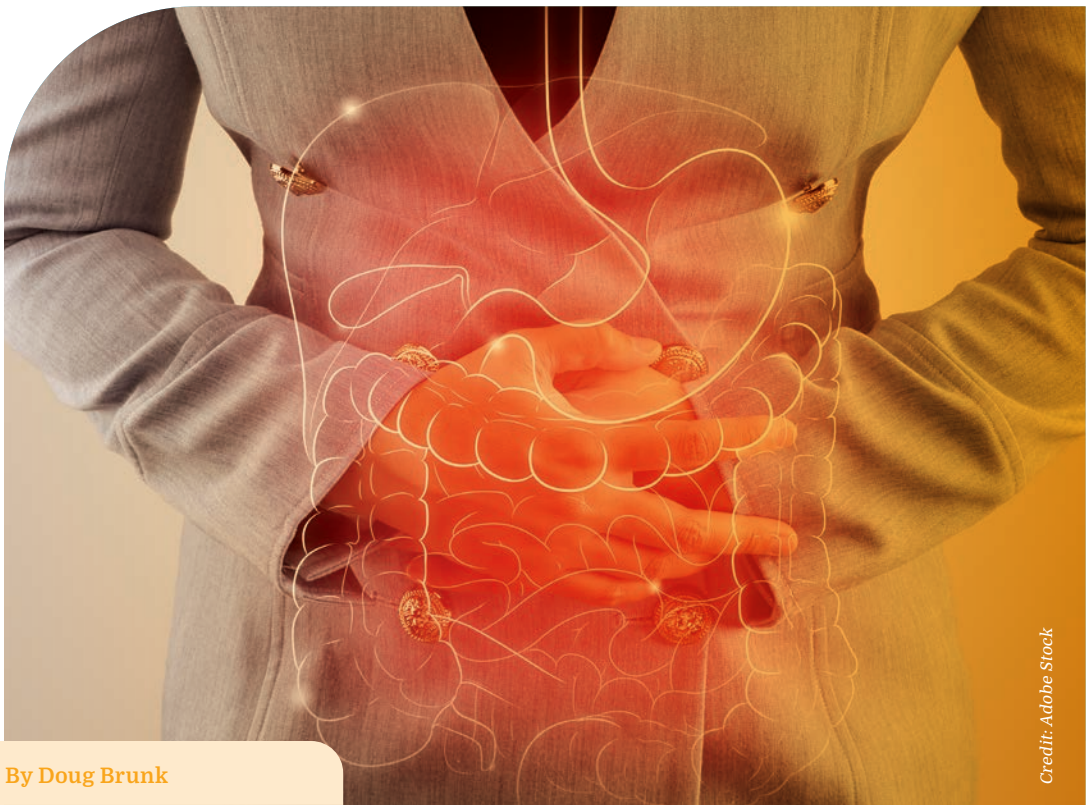

Credit: Adobe Stock

By Doug Brunk

# AGA releases practice update on refractory constipation

Longstanding concerns about chronic stimulant laxative use are described as unfounded.

AGA has released a clinical practice update outlining best practices for evaluating and managing refractory constipation, a challenging condition that affects a small but resource-intensive subset of patients. The expert review published in *Clinical Gastroenterology and Hepatology* emphasizes a systematic, pathophysiology-driven approach and urges clinicians to exhaust medical and behavioral therapies before considering surgery.

"This update is timely because refractory constipation remains an area of high clinical burden but relatively fragmented guidance," lead author Kyle Staller, MD, of the Division of Gastroenterology at Massachusetts General Hospital and Harvard Medical School, Boston, told *GI & Hepatology News*. "Most existing recommendations focus on chronic constipation broadly, yet clinicians increasingly encounter patients who have failed standard therapies and are being considered for irreversible surgical interventions. At the same time, there has been meaningful evolution in physiologic testing, availability of newer prescription agents, and emergence of non-pharmacologic therapies that may benefit this group of patients."

Continues · Page 9

## Single-molecule biosensor may enable earlier detection of high-risk pancreatic cysts

"We envision the use of SiMoT technology at the point of care for cyst fluid and especially blood-based testing in patients with clinically suspicious pancreatic cysts," noted the study authors.

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## Building effective community-based IBD care: Key challenges and opportunities

Most patients with inflammatory bowel disease (IBD) in the United States receive care in community practices that vary widely in size, staffing, and resources. Yet IBD management is becoming increasingly complex, driven by rising prevalence, an aging population, and rapidly evolving therapies.

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# HELP PATIENTS GET THE RELIEF THEY DESERVE

**INDICATIONS**[1]

**RINVOQ is indicated for the treatment of adults with:**

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

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

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

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

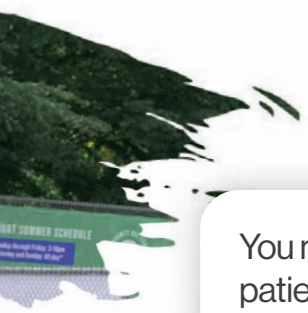
For adults with moderate to severe Crohn's disease (CD) or ulcerative colitis (UC) after inadequate response to a TNFi or another approved systemic therapy if a TNFi is clinically inadvisable[1]

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

RINVOQ®
upadacitinib

## ALSO AVAILABLE AFTER ANY BIOLOGIC OR ANOTHER APPROVED SYSTEMIC THERAPY

## if a TNFi is clinically inadvisable



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

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

## DO YOU HAVE PATIENTS WHO MAY BE RINVOQ READY?

## VISIT RINVOQHCP.COM/GASTROENTEROLOGY TO LEARN MORE

TNFi=tumor necrosis factor inhibitor.

**SAFETY CONSIDERATIONS[1]**

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

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

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

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

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

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

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

## IMPORTANT SAFETY INFORMATION[1]

### SERIOUS INFECTIONS

**Patients treated with RINVOQ are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants, such as methotrexate or corticosteroids. If a serious infection develops, interrupt RINVOQ until the infection is controlled.**

**Reported infections include:**

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

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

### MORTALITY

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

### MALIGNANCIES

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

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

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

### MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

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

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

### THROMBOSIS

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

### HYPERSENSITIVITY

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

### GASTROINTESTINAL PERFORATIONS

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

### LABORATORY ABNORMALITIES

**Neutropenia**

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

**Lymphopenia**

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

**Anemia**

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

**Lipids**

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

**Liver enzyme elevations**

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

### EMBRYO-FETAL TOXICITY

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

### VACCINATION

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

### MEDICATION RESIDUE IN STOOL

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

### LACTATION

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

### HEPATIC IMPAIRMENT

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

### ADVERSE REACTIONS

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

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

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

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

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

abbvie



RINVOQ®
upadacitinib

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

**PROFESSIONAL BRIEF SUMMARY**
**CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION**

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

**SERIOUS INFECTIONS**

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

**If a serious infection develops, interrupt RINVOQ/RINVOQ LQ until the infection is controlled.**

**Reported infections include:**

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

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

**Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with RINVOQ/RINVOQ LQ, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy *[see Warnings and Precautions]*.**

**MORTALITY**

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

**MALIGNANCIES**

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

**MAJOR ADVERSE CARDIOVASCULAR EVENTS**

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

**THROMBOSIS**

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

## INDICATIONS AND USAGE

### Rheumatoid Arthritis

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

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

### Ulcerative Colitis

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

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

### Crohn's Disease

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

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

## CONTRAINDICATIONS

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

## WARNINGS AND PRECAUTIONS

### Serious Infections

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

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

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

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

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

Tuberculosis

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

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

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

Viral Reactivation

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

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

### Mortality

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

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

### Malignancy and Lymphoproliferative Disorders

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

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

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

Non-Melanoma Skin Cancer

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

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

### Major Adverse Cardiovascular Events

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

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

### Thrombosis

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

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

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

### Hypersensitivity Reactions

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

### Gastrointestinal Perforations

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

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

### Laboratory Abnormalities

Neutropenia

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

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

Lymphopenia

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

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

Anemia

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

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

Lipids

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

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

Liver Enzyme Elevations

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

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

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

### Embryo-Fetal Toxicity

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

### Vaccinations

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

### Medication Residue in Stool

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

## ADVERSE REACTIONS

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

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

### Clinical Trials Experience

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

Adverse Reactions in Patients with Rheumatoid Arthritis

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

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

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

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

| Adverse Reaction | Placebo | 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 (6.4 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

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

The most frequently reported serious infections were pneumonia and cellulitis.

*Tuberculosis*

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

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

*Opportunistic Infections (excluding tuberculosis)*

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

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

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

*Malignancies*

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

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

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

*Gastrointestinal Perforations*

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

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

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

*Thrombosis*

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

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

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

*Laboratory Abnormalities*

*Hepatic Transaminase Elevations*

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

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

*Lipid Elevations*

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

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

*Creatine Phosphokinase Elevations*

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

*Neutropenia*

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

*Lymphopenia*

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

*Anemia*

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

Adverse Reactions in Patients with Ulcerative Colitis

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

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

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

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

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

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

* Composed of several similar terms

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

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

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

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

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

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

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

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

*Specific Adverse Reactions*

*Serious Infections*

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

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

*Laboratory Abnormalities*

*Hepatic Transaminase Elevations*

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

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

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

Adverse Reactions in Patients with Crohn's Disease

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

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

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

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

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

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

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

* Composed of several similar terms

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

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

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

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

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

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

*Specific Adverse Reactions*

*Serious Infections*

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

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

*Gastrointestinal Perforations*

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

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

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

## DRUG INTERACTIONS

**Strong CYP3A4 Inhibitors**

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

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

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

**Strong CYP3A4 Inducers**

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

## USE IN SPECIFIC POPULATIONS

**Pregnancy**

Pregnancy Surveillance Program

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

Risk Summary

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

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

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

Clinical Considerations

*Disease-Associated Maternal and/or Embryo/Fetal Risk*

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

Data

*Animal Data*

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

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

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

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

**Lactation**

Risk Summary

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

Data

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

**Females and Males of Reproductive Potential**

Pregnancy Testing

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

Contraception

*Females*

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

**Pediatric Use**

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

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

**Geriatric Use**

Ulcerative Colitis

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

Crohn's Disease

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

**Renal Impairment**

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

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

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

RINVOQ/RINVOQ LQ has not been studied in patients with end stage renal disease (eGFR <15 mL/min/1.73$m^2$). 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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# The evolving landscape of EoE management

From misdiagnosis to molecular insight, EoE has emerged as a chronic, immune-mediated disease with expanding diagnostic and therapeutic possibilities.

Once confused with refractory GERD, or simply dismissed as unexplained dysphagia, our collective understanding of eosinophilic esophagitis (EoE) as a distinct clinicopathologic entity has rapidly evolved during the past few decades. Since the mid-1990s, we have moved from initial case reports to a sophisticated appreciation of EoE's immunologic underpinnings, diagnostic criteria, and therapeutic targets.

Recent advances have illuminated EoE as a chronic, immune-mediated disease, tightly linked to environmental and genetic factors. We now recognize the central role of eosinophils and Th2-associated inflammation in the pathophysiology of EoE, leading to expanded therapeutic targets. Yet, even as diagnostic biomarkers and personalized treatments emerge, uncertainties remain.

While PPIs, dietary elimination, topical corticosteroids, and emerging biologics have given hope to patients, why do certain patients respond so differently to therapy? What is the natural history of EoE over decades, and what are the long-term outcomes of emerging therapies? And how can we reliably and objectively measure disease severity in both clinical trials and day-to-day practice? In this context, our February issue highlights emerging evidence supporting the clinical utility of I-SEE, a promising tool developed to bring clarity and consistency to assessment of EoE disease severity in both research and clinical care.

Also in this issue, we summarize AGA's recently released clinical practice update on management of refractory constipation and highlight a recent population-based study from *Gastroenterology* suggesting that routine screening for avoidant/restrictive food intake disorder (ARFID) in patients with DGBI may be beneficial due to its high prevalence in this patient population. This month's Member Spotlight features Dr. Oriana Damas (University of Miami), AGA FORWARD program graduate and 2025 Sherman Prize recipient, who discusses her fascinating research investigating the interplay between genetic and environmental risk factors in IBD, particularly among Hispanic populations. We also highlight AGA's IBD Care in the Community initiative, a society-sponsored effort to better understand the challenges of IBD management and identify opportunities for dissemination of integrated care models in community GI settings.

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

## Smart giving in 2026

Gastroenterology research creates successful practices, which means patients benefit from GI research daily in practices. Scientists are working hard to develop new treatments and to discover cures to advance the field and provide better patient care. But they can't do this without research funding.

If supporting young investigators through the AGA Research Foundation is important to you, consider these simple ways to give.

- **Grant from your donor advised fund (DAF).** This popular one-stop giving solution lets you care for multiple causes and organizations with minimal paperwork. And, when you use your existing DAF to recommend a grant, it means you can invest in the future of GI without impacting your budget today.
- **Distribution from your IRA.** When you are 70.5 or older, you can make a tax-free gift directly from your IRA to the AGA Research Foundation.
- **Gift in your will.** With as little as one sentence, you can create a brighter tomorrow for talented researchers funded by the AGA Research Foundation without parting with assets today. You can designate the AGA Research Foundation as the beneficiary of a specific asset or, as many of our donors do to ensure that their family is protected, as the recipient of a percentage of the total estate.
- **Beneficiary designation.** Adding the AGA Research Foundation as a beneficiary of your retirement plan or other assets is simple and can usually be completed entirely online in just a few minutes.

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# AGA releases practice update on refractory constipation

Continued From Page 1

For the update, Dr. Staller and coauthors Leila Neshatian, MD, Anthony Lembo, MD, and Adil E. Bharucha, MBBS, MD, developed Best Practice Advice statements to address 14 key clinical issues. According to Dr. Staller, three statements stand out as especially relevant to everyday practice:

1. It is recommended that most patients with chronic constipation undergo anorectal testing and pelvic floor biofeedback, when indicated, before being labeled as refractory. "Defecatory disorders remain common and frequently under-recognized, and failure to address them early can lead to unnecessary escalation and poor outcomes," he said. "Failure to adequately test for and treat these disorders is one of the most common causes for refractory symptoms that I see in my tertiary referral practice."

2. Objectively documenting slow colonic transit — ideally both off therapy and on maximal therapy — before considering surgical options is emphasized. "Symptoms alone are insufficient to guide major interventions, and physiologic confirmation is critical," he said.

3. Recommendations for surgical patient selection include evaluation of upper gastrointestinal dysmotility and psychological comorbidities. According to Dr. Staller, these factors "substantially influence outcomes and are essential components of preoperative assessment," he said. "Since constipation can reflect both motor and sensory dysfunction, realizing that these disorders commonly affect other parts of the GI tract and central nervous system is key."

Another practice advice statement calls for clinicians to look beyond the gut for secondary causes of constipation such as medications, disordered eating, endometriosis, or comorbid neurological diseases such as Parkinson's disease or multiple sclerosis. "Medications are among the most common iatrogenic causes of chronic constipation including opioid-induced or opioid exacerbated constipation," the authors wrote. "Other frequent secondary causes include anticholinergic agents such as antipsychotics and iron supplements."

The update strongly encourages optimization of medical therapy before escalating care. In addition to FDA-approved agents such as linaclotide, plecanatide, and prucalopride, the authors support rational combination therapy using agents with different mechanisms of action. Longstanding concerns about chronic stimulant laxative use are described as unfounded, which Dr. Staller said may surprise some clinicians. "Additionally, the growing role of non-pharmacologic interventions — such as vibrating capsules, electroacupuncture, and transanal irrigation — may be unexpected, particularly for clinicians trained when therapeutic options were far more limited," he said.

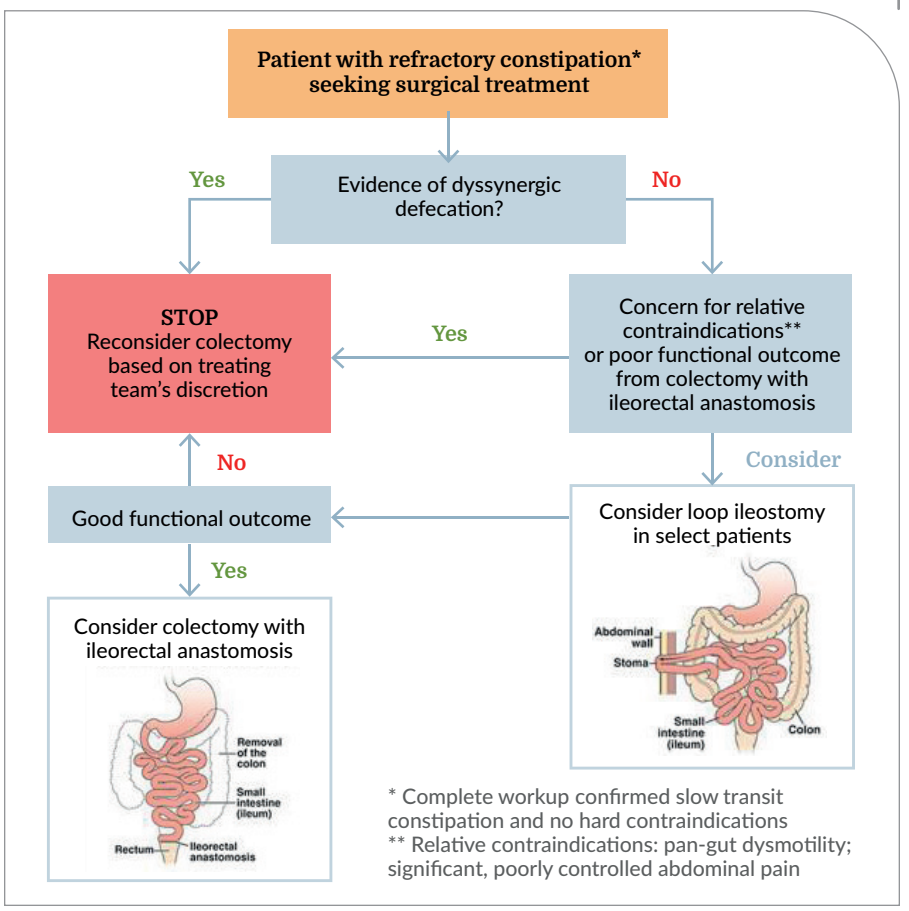
According to Dr. Staller, surgical management generated the most discussion during development of the practice update. While colectomy can be effective in carefully selected patients, "it is also associated with significant morbidity and variable long-term satisfaction," he said. "Determining how strongly to frame recommendations around relative contraindications, psychological assessment, and the role of temporary diversion required careful consideration. We wanted to be clear and evidence-based without oversimplifying a complex clinical decision."

He and his coauthors also discussed how to position off-label and non pharmacologic therapies. "Although the evidence base is still evolving, these approaches are increasingly used in practice, and we felt it was important to provide clinicians guidance since we all use these approaches in our own practices," he said

The authors acknowledged that significant knowledge gaps remain in the optimal management of refractory constipation, including the lack of reliable predictors of treatment response, particularly for advanced pharmacologic therapies and surgical interventions. They also called for comparative studies evaluating combination treatments and integrated medical and behavioral strategies.

"Finally, longer-term outcomes data for newer agents and device-based therapies, as well as more work on the interaction between psychological factors and motility, would meaningfully advance the field," Dr. Staller said.

*Dr. Staller was supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases. He and his coauthors disclosed being a consultant for and/or receiving research funding from several pharmaceutical companies.*




Courtesy Dr. Staller

*"Failure to adequately test for and treat these disorders is one of the most common causes for refractory symptoms that I see in my tertiary referral practice."*

Kyle Staller, MD

**Video: Evaluation and management of refractory constipation**

Scan the QR code to view online.

# ‘Chaos scheduler’ boosts endoscopy utilization

“We were surprised by how much of an impact just one additional staff member on our scheduling team was able to have on the utilization rate at our endoscopy centers.”

By Doug Brunk

The demand for gastrointestinal (GI) endoscopic procedures is steadily rising, fueled by expanding procedural capabilities and updated screening guidelines. At the same time, practices are grappling with access to specialists, anticipated workforce shortages, and declining reimbursements from both commercial insurers and government payers. Together, these pressures underscore the need for more efficient scheduling within endoscopy units to accelerate patient access, reduce delays, and keep practices operating smoothly.

In a practice management review published in *Clinical Gastroenterology & Hepatology*, first author Joshua L. Hudson, MD, a gastroenterologist and Director of Clinical Operations in the Division of Gastroenterology & Hepatology at the University of North Carolina (UNC) School of Medicine, and colleagues highlighted previously reported strategies for improving endoscopy scheduling and throughput, and shared their own experiences at UNC, a large tertiary-care academic medical center.

In their review, the authors noted that existing recommendations to optimize endoscopy unit performance in terms of scheduling are largely conceptual, with few studies reporting measurable outcomes.

For example, a discrete-event simulation study at Zuckerberg San Francisco General Hospital demonstrated potential efficiency gains in the pre-procedure area and post-anesthesia care unit (PACU). Adding staff in the pre-procedure area increased procedural volume by 14.6 cases per week, while reducing PACU recovery times to 30 minutes could yield an additional 13.8 cases per week.

To address these gaps, the authors shared their own experience improving pre-procedure workflows at UNC, highlighting practical ways to make targeted changes within the routine operations of an endoscopy unit.

Successful strategies include:

1. **Standardized protocols and forms:** The authors created a uniform anti-thrombotic form that provides guidance on commonly used anticoagulants and antiplatelet agents, including recommended hold ties, to facilitate consistent practice. Forms can be shared electronically or embedded in the electronic medical record using SmartPhrases, allowing referring providers to document relevant information efficiently.

2. **Dedicated antithrombotic workflow:** Patients on anticoagulants or antiplatelet therapy can be triaged into a dedicated queue managed by trained nurses who coordinate with the prescribing provider. Once the necessary documentation is received, patients can be transitioned to a “ready-to-schedule” queue, ensuring clarity and reducing delays.

3. **Enhanced patient communication:** Clear instructions regarding medication management can be provided through electronic messaging or patient portals, supporting adherence and improving patient safety.

Last-minute appointment cancellations are another common headache for endoscopy units. At UNC, an average of 12 endoscopic procedures per week were unfilled due to cancellations that occurred 1–3 days before the date of service, a term the authors referred to as the “chaos period.” To address this, the authors hired a dedicated “chaos scheduler” whose only responsibility is to reassign cancelled slots.

Joshua L. Hudson, MD

From the launch of the chaos scheduler model at UNC, 89% of patients successfully completed procedures. Weekly, an average of 11.7 slots that would have remained vacant were filled, increasing utilization in ambulatory endoscopy units from 83% to 87% to consistently above 95%. In higher-complexity units, utilization improved from 88% to 92%. The authors estimate that over the course of a year, this approach could allow 550 to 600 more procedures to be completed without needing major new equipment or facilities.

“We were surprised by how much of an impact just one additional staff member on our scheduling team was able to have on the utilization rate at our endoscopy centers,” Dr. Hudson said in an interview with *GI & Hepatology News*. “Particularly at our high-volume, ASC-like unit, the addition of the ‘chaos scheduler’ significantly improved room utilization. While hiring a new staff member is an investment, this was and remains an investment that has paid dividends back to our practice and to patient access.”

At the same time, the authors introduced an automated reminder system using both phone calls and electronic messaging to reduce no-shows and same-day cancellations.

In Dr. Hudson’s opinion, a key take-home message of the review “is to work closely with your endoscopy scheduling teams and listen to their input and feedback,” he said. “Much of the processes for our practice surrounding the ‘chaos scheduler’ and scheduling standardization came from our scheduling team. Their ongoing leadership has been key to the success of these measures.”

*The researchers reported having no financial disclosures.*

# ACA expansion linked to better liver disease outcomes

The analysis is believed to be the first of its kind.

By Doug Brunk

Lauren D. Nephew, MD, MSCE

The Affordable Care Act (ACA), especially its Medicaid expansion (ME), has helped people with chronic liver disease who qualify for Medicaid get better access to care, live longer, and experience fewer health disparities, according to a new review.

"The findings are especially timely as several states still have not expanded Medicaid and millions of patients are losing coverage following the unwinding of pandemic-era continuous enrollment," the study's senior author, Lauren D. Nephew, MD, MSCE, Assistant Professor of Medicine in the Division of Gastroenterology and Hepatology and the Assistant Vice Chair of Health Equity at Indiana University School of Medicine, told *GI & Hepatology News*. "Liver disease disproportionately affects socially marginalized populations. Demonstrating that Medicaid expansion improves early cancer detection, transplant access, survival, and equity provides strong evidence that insurance policy is a powerful lever for improving liver-related outcomes at the population level and for reducing health disparities."

In what the authors describe as the first analysis of its kind, reported in *Clinical Gastroenterology and Hepatology*, Dr. Nephew and colleagues reviewed studies published between 2010 and 2025 that included adults with chronic liver disease and evaluated ACA/ME effects on access to services, survival and mortality, and disparities in outcomes. They focused on 27 studies that compared outcomes between ME and non–Medicaid Expansion (NME) states before and after ACA implementation and used the validated Cochrane Risk of Bias in non-Randomized Studies of Interventions tool to assess the quality of studies included.

The 27 studies spanned four clinical categories: hepatitis C virus, liver transplantation, hepatocellular carcinoma, and cirrhosis or chronic liver disease. Twenty-three studies reported improved outcomes associated with ACA/ME and most met criteria for low-to-moderate risk of bias and used causal inference methods. Difference-in-difference analyses identified the following trends for each clinical category:

- HCV studies showed improved access to direct-acting antiviral therapy in ME states. Expansion states consistently reported higher direct-acting antiviral prescription rates and Medicaid reimbursement levels compared with NME states.

- Liver transplantation listing increased by 1.8% to 6% in ME versus NME states. Black and Hispanic patients experienced significantly larger increases in Medicaid-supported waitlisting in ME states, suggesting partial mitigation of long-standing access barriers. However, improvements in transplant rates were not observed across racial subgroups.

- Findings on early-stage diagnosis of hepatocellular carcinoma and receipt of curative therapy were mixed, likely due to differences in data sources and analytic methods, with some studies showing improved early detection and surgical treatment in ME states and others finding no significant stage shift.

  However, survival outcomes improved more consistently in ME than in NME states after ACA implementation (median overall survival, 7.3 months versus 4.5 months, respectively), with particularly large gains among non-Hispanic Black patients and rural populations.

- Of the five studies that examined chronic liver disease and cirrhosis, ME was associated with lower emergency department readmissions, shorter hospital stays, and reduced hospitalization costs. At the population level, mortality related to chronic liver disease continued to increase nationwide, but the rate of increase was substantially slower in ME states. Difference-in-differences analyses showed mortality growth of 0.5–1 per 100,000 in ME states versus 1.4–10.4 per 100,000 in NME states, translating into hundreds of potentially preventable deaths annually.

Dr. Nephew characterized the consistency of ACA benefit across different clinical domains as striking. "Seeing such alignment across transplantation, oncology, and chronic disease management reinforces that insurance coverage fundamentally shapes access and outcomes," she said. "The equity gains were [also] notable. Several studies demonstrated narrowing racial and ethnic disparities, particularly for Black and Hispanic patients in transplant access and cancer survival."

She added, the findings underscore that insurance access is a core determinant of timely, high-quality care, not a peripheral factor in clinical outcomes. "Providers should recognize that their patients face systemic barriers that cannot be overcome solely through individual clinical decision-making and think through what options they have at the clinic and health-system level to mitigate insurance barriers," Dr. Nephew said. "More broadly, the results empower clinicians and professional societies to engage in policy advocacy, recognizing that coverage decisions directly affect survival and equity for patients with liver disease."

*The study was funded by grants from the National Institute on Minority Health and Health Disparities and the National Institute of Diabetes and Digestive and Kidney Diseases. The authors had no disclosures to report.*

# Single-molecule biosensor may enable earlier detection of high-risk pancreatic cysts

The device is designed to detect biomarkers at extremely low concentrations, delivering rapid results.

By Doug Brunk

A single-molecule biosensor in development could enable earlier, less invasive identification of high-risk pancreatic cysts through analysis of cyst fluid samples.

"Early detection of pancreatic cancer represents the only chance for cure of this extraordinarily aggressive disease," Irene Esposito, MD, of the Institute of Pathology at Heinrich-Heine University and University Hospital of Dusseldorf, Germany, and colleagues wrote in *Gastro Hep Advances*. "This implies the detection and surgical resection of high-risk cystic lesions, that is, intraductal papillary mucinous neoplasms and mucinous cystic neoplasms bearing high-grade dysplasia. Application of multidisciplinary guidelines has improved the detection of high-risk precursors, but the proportion of false negative and false positive cases remains high."

Irene Esposito, MD

Luisa Torsi, PhD

To address these gaps, the authors evaluated the Single Molecule Bio-Electronic Smart System Array for Clinical Testing (SiMBiT), a novel portable diagnostic platform based on single-molecule-with-a-large-transistor (SiMoT) technology. The device is designed to detect molecular biomarkers at extremely low concentrations, delivering rapid results without the need for extensive sample processing or sequencing.

The researchers analyzed 92 liquid samples (73 pancreatic cyst fluids and 19 plasma samples) collected consecutively from 82 patients undergoing routine evaluation for newly diagnosed pancreatic cystic lesions. After applying predefined quality criteria, 79 samples from 71 patients were included in the final analysis. The researchers used a multidisciplinary approach for diagnoses, integrating clinical features, imaging, cytology or histology when available, and next generation sequencing-based cyst fluid analysis.

Among 61 cyst fluid samples, SiMBiT demonstrated strong performance for identifying mucin-producing cystic neoplasms, misclassifying only three cases. Sensitivity was 91%, specificity 99%, and both positive and negative predictive values were 95%.

Performance was higher for detecting high-grade dysplasia. All high-grade lesions in cyst fluid were correctly identified. Even when two indeterminate cases were conservatively considered false positives, sensitivity remained 100% and specificity 96%, with a negative predictive value of 100%.

In blood alone, SiMBiT achieved 100% sensitivity and 100% specificity for detection of high-grade mucin-producing neoplasms in this small cohort. If validated in larger studies, these results suggest that a simple blood test could identify patients harboring clinically significant pancreatic cysts—potentially reducing the need for invasive EUS-guided sampling in a substantial subset of patients.

"We envision the use of SiMoT technology at the point of care for cyst fluid and especially blood-based testing in patients with clinically suspicious pancreatic cysts," the authors concluded. "The clinical decision should always occur in the context of multidisciplinary expertise, considering the still high rates of morbidity and mortality of pancreatic surgery, which would follow a positive result."

*This project has received funding from the European Union's Horizon 2020 research and innovation program. The authors reported having no disclosures.*

*GI & Hepatology News* invited Dr. Esposito and Torsi to comment on their work.

**What makes this study important, and what unmet gaps in knowledge or therapeutics does it address?**

This work is important because it tackles a central bottleneck in pancreatic cancer prevention: identifying which pancreatic cystic lesions are truly high-risk (high-grade dysplasia and/or incipient cancer) early enough to enable curative intervention — while avoiding unnecessary invasive procedures and surgery for low-risk lesions. Current guideline-based management and conventional workups still leave substantial false positives and negatives, and advanced molecular approaches (e.g., broad NGS [Next Generation Sequencing] panels) can be accurate but are costly and typically restricted to specialized centers, limiting accessibility. By leveraging the SiMBiT prototype platform, the study addresses an unmet diagnostic gap: a rapid, portable, multiplex, minimally invasive test that can read out both genetic and protein biomarkers at the single molecule limit-of-identification, with the design goal of keeping false positives and negatives very low, in principle below 1%.

**What are the possible clinical implications of this research?**

In clinical terms, the results suggest that this technology could meaningfully improve the way pancreatic cystic lesions are evaluated, particularly by enabling blood-based-test risk stratification. From a practical standpoint, the work also points toward realistic point-of-care implementation. The SiMBiT approach is based on a disposable, ELISA-like cartridge integrating 96 independent sensors, coupled to a reusable electronic reader, with a workflow designed for near-patient testing and rapid turnaround.

**What further research is needed, and what gaps in knowledge remain?**

Key next steps are primarily translational and clinical in nature. Larger prospective, multi-center studies will be needed to validate these findings in well-defined patient populations, using standardized reference standards, in order to narrow confidence intervals and confirm that the performance observed to date is robust and generalizable.

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

Two broader points are worth emphasizing. First, this work underscores the importance of a truly multiparametric view of disease biology. Rather than relying on a single type of biomarkers, the strategy deliberately integrates a key genomic alteration, such as KRAS with protein markers associated with malignant transformation and disease aggressiveness, including MUC1 and CD55. This combined molecular readout is designed to better reflect the biological complexity of pancreatic cystic lesions and to overcome the well-known limitations of single type-marker approaches in supporting real clinical decision-making. Second, accessibility is a core scientific and translational objective of the SiMBiT effort. From the outset, the project has aimed to translate single-molecule bioelectronic sensing into a cost-effective, portable diagnostic format with rapid time-to-result, rather than confining ultra-high sensitivity to specialized research laboratories. This focus on decentralization and practicality is intended to enable deployment in a wide range of clinical settings, including environments with limited resources, thereby broadening access to high-performance diagnostics.

# When gut-brain disorders affect eating in adults

"Restrictive eating in DGBI is common beyond specialist clinics and highlights the need for integrated multidisciplinary care."

By Doug Brunk

Imran Aziz, MBChB, MD

About one in three adults in the general population who have disorders of gut–brain interaction (DGBI) also show signs of avoidant/restrictive food intake disorder (ARFID), according to what researchers believe is the first survey of its kind.

"This study validates that restrictive eating in DGBI is common beyond specialist clinics and highlights the need for integrated multidisciplinary care to optimize patient outcomes," senior author Imran Aziz, MBChB, MD, a consultant gastroenterologist at the University of Sheffield, United Kingdom, told *GI & Hepatology News*.

For the study, published in *Gastroenterology*, researchers conducted a population-based internet survey of 4,002 adults in the United Kingdom and United States in 2023. They presented the survey as a "general health" study to minimize selection bias related to GI or eating disorder symptoms and used validated instruments, including the Rome IV Diagnostic Questionnaire for DGBI and the Nine-Item ARFID Screen (NIAS), and asked questions about demographics, body mass index, non-gastrointestinal somatic symptoms, anxiety and depression, quality of life, and health care use.

The mean age of the study population was 46 years and half were female. The researchers found that 42.6% of respondents experience symptoms of DGBI. Women were more likely to be affected than men (48.3% vs 36.9%), and the median age of those with DGBI was younger at 42 years, compared with 49 years for those without symptoms. One in four respondents (24.8%) had symptoms in one region of the digestive tract, 11.7% in two regions, 4.3% in three regions, and 1.7% in all four regions.

Among individuals with DGBI, 34.6% screened positive for ARFID. This prevalence was significantly higher than in those without DGBI (19.4%), even after adjusting for age, sex, ethnicity, and mood disorders. All three ARFID symptom domains were more common in DGBI: lack of interest in eating (21.5%), sensory-based avoidance (18.1%), and fear of aversive consequences such as pain, nausea, or vomiting (9.9%).

The prevalence of ARFID symptoms increased stepwise with DGBI complexity. Only 27.7% of individuals with one affected GI region screened positive, compared with 50% of those with three regions and 61.4% of those with four. Functional dyspepsia and irritable bowel syndrome were particularly associated with ARFID symptoms, with roughly half of patients screening positive.

In other findings, individuals with DGBI plus ARFID, compared with those with DGBI alone, were significantly more likely to be underweight (7.9% vs 1.5%, respectively). They also had higher rates of anxiety (51% vs 33%), depression (49.2% vs 32%), somatic symptoms (63.7% vs 43.1%), doctor visits (14.7% vs 9.6%), and medication use (83.7% vs 72.4%).

"Clinicians should routinely screen DGBI patients for ARFID, starting with an open-ended question like 'tell me about your relationship with food' or a brief 24-hour dietary recall," Dr. Aziz advised. "Validated questionnaires such as the nine-item ARFID screen can also be used. If positive or concerned, clinicians should consider multidisciplinary care involving dietitians and psychologists."

The researchers acknowledged certain limitations of the study, including the lack of gender minority groups and the lack of access of medical records to confirm self-reported data. "Longitudinal studies are needed to determine whether DGBI causes ARFID, or vice versa," Dr. Aziz added. "Randomized trials testing multidisciplinary interventions and cognitive behavioral therapy for co-occurring DGBI and ARFID are also essential."

*The survey was funded by Tillotts Pharma and Novonesis and supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases. One of the study authors reported receiving royalties from Oxford University Press and Cambridge University Press. The remaining authors disclosed no conflicts.*

## Data reinforces addressing food-related fear

*GI & Hepatology News* invited Madison L. Simons, PsyD, a GI psychologist in the Department of Gastroenterology, Hepatology, and Nutrition at Cleveland Clinic, to comment on the study.

**Why is this research important?**

**Dr. Simons:** The existing research on ARFID in GI conditions has been specific to certain tertiary care centers where typically patients with more severe GI conditions are being treated. As a population-based study, this study is different in that it provides more generalizable data about the likely prevalence of ARFID among patients with disorders of gut brain interaction. This data replicates what has been found across tertiary care centers, which is that a third of patients with DGBIs screen positive for ARFID based on a brief screening measure. Compared to other studies in GI patients, patients were more likely to screen positive for ARFID based on lack of interest in eating compared to fear of the aversive consequences of food and eating (such as nausea, vomiting, diarrhea, etc.), which may suggest there are differences in the types of patients that seek medical care for their GI symptoms.

**What are the potential clinical implications of the research?**

**Dr. Simons:** This study provides further evidence demonstrating the impact of DGBIs on patients' relationship with food and eating. Unfortunately, this is often not a primary focus of DGBI treatment unless patients are being seen in a center that is able to deliver true multidisciplinary care between medicine, psychology, and nutrition. These findings highlight that it is of critical importance to be talking to patients about how their GI condition affects their relationship with food and eating.

Madison L. Simons, PsyD

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

**Dr. Simons:** We would still benefit from being able to predict who is at risk of developing ARFID in the context of a digestive condition. We know that there are differences between those with and without ARFID in terms of things like BMI, healthcare utilization, presence of other somatic symptoms, etc., but we do not yet have a way of identifying who could be likely to develop ARFID once their GI symptoms begin, which could help us provide earlier intervention.

A primary research priority for ARFID is the development of effective and scalable treatments for ARFID among patients with GI conditions. This research highlights the immense number of DGBI patients who exhibit symptoms of ARFID, in comparison to the dearth of specialized providers available to treat this condition. While treatments are administered in eating disorder centers for ARFID that does not occur in the context of a GI condition, there are unique medical considerations that DGBI patients have that need to be attended to during ARFID treatment. Effective ARFID treatment is not available in many centers right now; we need a way to expand access to this treatment.

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

**Dr. Simons:** The ongoing struggle we have around ARFID in GI is that we continue to rely on measures like the Nine-Item ARFID Screen to identify those who exhibit symptoms of ARFID. While the NIAS can tell us certain features of a patient's relationship with food, I think there are more nuances around the eating experience that are not captured, such as hypervigilance around diet or the actual foods consumed and overall dietary pattern. I am hoping in the coming years we can further refine our perspective of ARFID such that it does not over pathologize eating behaviors while also being able to accurately identify those in need of additional support.

# Navigating PSC: Diagnosis and the 5 pillars of management

Primary sclerosing cholangitis (PSC) remains a challenging disease to diagnose and manage, due to varying presentations, associated disease processes, and lack of targeted treatment.

In this issue's In Focus, Drs. Mahesh Krishna and David N. Assis describe the diagnostic approach when PSC is suspected. Once diagnosed, they emphasize the five pillars of managing patients with PSC: malignancy, infection, fibrosis, symptoms, and inflammatory bowel disease activity.

*Judy Trieu, MD, MPH, Editor in Chief*
*The New Gastroenterologist*

## Approach to primary sclerosing cholangitis

By Mahesh Krishna, MD, and David N. Assis, MD

### What is primary sclerosing cholangitis?

Primary sclerosing cholangitis (PSC) is a chronic autoimmune liver disease characterized by inflammation and fibrosis of the intra- and extrahepatic bile ducts.[1] A significant source of the morbidity and mortality in PSC consists of the elevated risk of malignancy, including cholangiocarcinoma, colorectal cancer, and gallbladder cancer[2] Disease progression in PSC is difficult to predict as there are no validated surrogate markers for clinical outcomes, such as cirrhosis, death, or cancer.

Patients with PSC often have elevated levels of alkaline phosphatase (ALP), a serum marker of cholestasis that is often used to assess clinical disease activity. However, ALP is limited by significant inter and intra-individual variation, and therefore may not consistently prognosticate disease progression.[3] Emerging prospective data from the FICUS study by the International PSC Study Group evaluated transient elastography (TE) for liver stiffness measurement (LSM), to predict outcomes in PSC.[4] First presented at EASL 2024, data showed that LSM by TE was strongly and independently correlated with overall survival and need for liver transplantation. Specifically, transplant-free survival at 5 years was 93.8% with LSM < 9.3 kPa, 79% with 9.6-14.3 kPa, and 48.1% with > 14.4 kPa, suggesting that LSM should be routinely incorporated into the clinical care and risk-stratification of patients with PSC.[5]

### When should PSC be suspected?

The typical demographic of PSC was traditionally thought to be that of a young adult male. Indeed, most patients are male, an unusual demographic for an autoimmune disease. However, PSC can present at any age and in any sex, race, or ethnicity; and so it should be suspected in anyone with suggestive clinical signs or symptoms.[6] About half of patients are asymptomatic at diagnosis, but the most common presenting symptoms within the first few years of diagnosis include fatigue, abdominal pain, pruritus, and depression.[1]

The diagnostic modality of choice in PSC is magnetic resonance cholangiopancreatography (MRCP) with the typical features including intra- and/or extra-hepatic strictures alternating with normal or dilated bile ducts, although a negative MRCP does not exclude PSC in the setting of high pretest probability.[7] Due to the advancements in MRCP imaging quality and non-inferiority of MRCP for PSC diagnosis, ERCP is not recommended for diagnosis along with procedural risks of pancreatitis and biliary tract seeding.[7] PSC should be suspected in any patient with elevation in cholestatic enzymes such as ALP or γ-glutamyltransferase, especially in a patient with pre-existing IBD. 4 PSC has a very strong association with inflammatory bowel diseases (IBD), detected in up to 80% of cases, while approximately 5% of patients with IBD have PSC.[1] PSC-IBD has unique characteristics of intestinal inflammation including higher prevalence of extensive colitis, worsened right-sided colonic disease with backwash ileitis, and clinically mild disease. Colitis in PSC-IBD also significantly increases the risk of colorectal cancer compared to IBD alone.[1,8] Therefore, PSC-IBD should be considered a unique clinical entity, and the standard manifestation of the disease.

Furthermore, in one cohort study that empirically screened all IBD patients with MRCP, up to 7.5% had biliary PSC-like strictures, even though many had no symptoms nor laboratory abnormalities[9]. However, preemptive MRCP screening of IBD patients, in the absence of abnormal cholestatic labs or symptoms, is not currently recommended. Interestingly, the rate of IBD in African American patients with PSC is lower (60%) compared to the general population (80%), so there should be a lower threshold to suspect PSC in this demographic with elevated cholestatic enzymes, even without intestinal inflammation.[6] In patients without IBD, causes of secondary sclerosing cholangitis should be closely scrutinized and ruled out such as HIV, ischemia, malignancy, IgG4 disease, sarcoidosis, and immunotherapy related diseases.[7] According to AASLD practice guidance, and EASL practice guidelines, all patients with suspected PSC should have serum IgG4 levels obtained once to rule out IgG4-sclerosing cholangitis.[7,10]

Small-duct PSC is denoted by histological findings of PSC on liver biopsy in the absence of biliary strictures on MRCP and clinical presentation is similar to large-duct PSC although small-duct PSC does not have the risk of acute biliary obstruction or cholangitis.[7] Small-duct PSC carries a more favorable prognosis but can develop into large-duct PSC in up to a quarter of patients.[7] Therefore, MRCP should be repeated every 3-5 years for these patients.[7]

### How should PSC be managed?

There are currently no FDA-approved treatments for PSC. Historically, ursodeoxycholic acid (UDCA) was repurposed from PBC for patients with PSC. The initial randomized controlled trial of UDCA in PSC, published in the New England Journal of Medicine in 1997, showed that 13-15 mg/kg of UDCA improved ALP, total bilirubin, and aspartate aminotransferase at 1 and 2 years.[11] However, there was no difference in overall transplant-free survival, nor has this been demonstrated in subsequent trials. One clinical trial using high-dose UDCA (28-30 mg/kg) reported an increased rate of adverse events, and this dosing should not be used.[7,11]

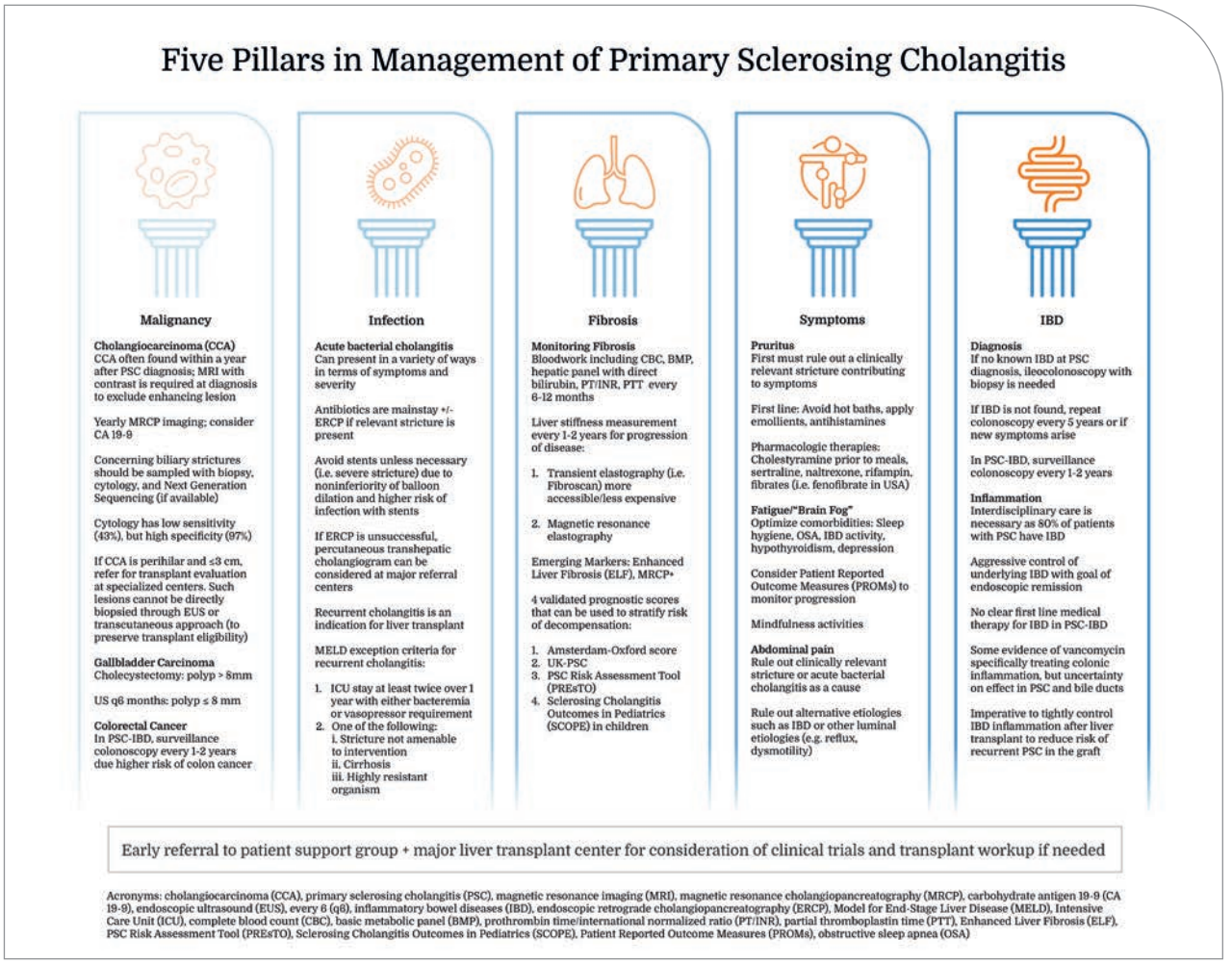
Due to the lack of effective therapy, all patients with PSC should be referred to specialized centers for consideration of enrollment in clinical trials. If a patient with elevated cholestatic serum tests is not eligible or interested in clinical trials, moderate UDCA doses (13-23 mg/kg/day) can be prescribed to reduce cholestatic markers, given that reduced cholestatic markers may impact long-term outcomes in some patients based on retrospective data.[12,13] However, this should not substitute for the urgent need for innovative therapies in PSC, and many recent clinical trials allow patients treated with ongoing UDCA to enroll. There are five pillars (Figure 1) that every clinician should be mindful of when managing patients with PSC: malignancy, infection, fibrosis, symptoms, and IBD activity.

**Malignancy.** The first major pillar of PSC management includes screening for malignancy due to a significantly higher risk compared to the average population. Cholangiocarcinoma is the most feared complication of PSC with the highest

risk within the first year of diagnosis and up to a 20% risk of the cancer at 30 years after diagnosis.[7] Guidance from the AASLD recommends MRCP with or without carbohydrate antigen 19-9 (CA 19-9) yearly to monitor for the development of cholangiocarcinoma. CA 19-9 is neither fully specific or sensitive for cholangiocarcinoma and often will be elevated at baseline in patients due to cholestasis. However, when combined with MRCP, a CA 19-9 cutoff of 20 U/mL may increase the sensitivity up to 100%, while a cutoff of 129 U/mL may actually have a specificity up to 98%.[7] In contrast, EASL guidelines recommend against checking a CA 19-9 due to it limited accuracy, though yearly imaging with MRCP is recommended.[10] In patients with cirrhosis, more frequent imaging to monitor for hepatobiliary malignancy, including hepatocellular carcinoma, is recommended every 6 months.[10]

Patients with PSC also have an elevated risk of gallbladder carcinoma (9-78 times greater than the general population) and attention should be given to the gallbladder on yearly imaging.[7] Patients with a gallbladder polyp >8 mm should be immediately referred for an evaluation for cholecystectomy while those with a polyp ≤8 mm should have surveillance ultrasound imaging every 6 months.[7]

Patients with PSC-IBD also have an increased risk of colorectal cancer compared to the general population and compared to patients with IBD alone. Colonoscopy with segmental biopsies should be performed at diagnosis of PSC to rule out concomitant IBD, if not already diagnosed.




Courtesy Dr. Krishna and Dr. Assis

**Infection.** The second major pillar in managing PSC is the treatment of infections such as bacterial cholangitis, a common complication of the disease due to biliary strictures and bacterial colonization of the biliary tree. Bacterial cholangitis can present in a variety of ways and there is currently no consensus definition for a true episode of bacterial cholangitis in PSC. The presentation of acute cholangitis typically includes abdominal pain, fevers, and jaundice; however not all patients present with classic findings of the Charcot's Triad and thus the threshold to suspect cholangitis in PSC should be low. Some patients present with sepsis and bacteremia. Others present with less severe fevers and elevated cholestatic markers, while the mildest cases display only minor symptoms that are relieved with antibiotics.[10] Oral amoxicillin/clavulanic acid is often administered for milder cases, while piperacillin/tazobactam or a third generation cephalosporin with anaerobic coverage is used in cases of bacteremia requiring intravenous antibiotics.[10] Temporary biliary stents are often necessary for management of severe strictures, though for milder strictures, they should be avoided due to their non-inferiority to balloon dilation but increased risk of bacterial cholangitis.[14]

**Fibrosis.** The third pillar is monitoring for signs of liver fibrosis progression to cirrhosis. Patients with PSC should receive bloodwork every 6-12 months monitoring liver enzymes including aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total and direct bilirubin, albumin level, γ-glutamyltransferase as well as a complete blood count (monitoring platelets closely) and basic metabolic panel (monitoring sodium and creatinine), as well as a coagulation panel. Per EASL guidelines, LSM, either by TE or magnetic resonance elastography, should be performed every 2-3 years to monitor for progression of disease.[10] Based on emerging data, it is reasonable to monitor with a LSM yearly, due to its validated prognostic value[6]. Another emerging option, not yet widely available, is serum fibrosis testing with the Enhanced Liver Fibrosis (ELF) score, comprising of serum markers associated with fibrosis development such as hyaluronic acid, tissue inhibitor of metalloproteinase-1, and procollagen type III N-propeptide. Currently, there is an effort by the International PSC Study Group, funded by PSC Partners Seeking a Cure, to validate ELF as a prognostic marker of clinical outcomes, similar to the FICUS study with TE. One other option to monitor risk of hepatic decompensation or liver transplantation is to utilize a validated clinical prognostic model for PSC such the Amsterdam-Oxford score, UK-PSC, and PSC Risk Assessment Tool (PREsTO) for adults and Sclerosing Cholangitis Outcomes in Pediatrics (SCOPE) for children.[7] However, these tools should be used with caution in individual patients until further validation. Patients with cirrhosis should be referred to a transplant center with experience in PSC.

**Symptoms.** Addressing symptoms such as pruritus, fatigue, "brain fog", and abdominal pain comprise the fourth pillar of PSC management. Pruritus can occur with or without biliary strictures, but new onset of itch should prompt laboratory studies and an MRCP for evaluation of a culprit clinically-relevant stricture. First line management should include counseling on avoiding heat and hot baths, utilizing topical emollients, and antihistamines such as hydroxyzine. If these are ineffective, therapy with a bile acid sequestrant, such as cholestyramine (4-16 mg), can be attempted, though it is associated with gastrointestinal side effects.[7] Other options for pruritus not responsive to initial management include sertraline, naltrexone, and rifampin.[7] Importantly, the FITCH trial recently demonstrated that fibrates, such as fenofibrate and bezafibrate (not available in the U.S.), are effective at reducing cholestatic itch in patients with PBC and PSC15 and this option should also be considered. Lastly, ileal bile acid transporter inhibitors (IBAT-i) are an emerging therapy for management of cholestatic pruritus in PBC and PSC.[16]

Fatigue and "brain fog" are much more difficult symptoms to manage with optimization of other potential underlying causes such as sleep hygiene, obstructive sleep apnea, and hypothyroidism as good initial steps. Other techniques such as mindfulness have previously been shown to improve symptoms in patients with autoimmune hepatitis and similar programs are under active investigation in PSC.[17]

Right upper abdominal pain is also a frequent symptom in patients with PSC, and the first step of management is to rule out worsening biliary obstruction or acute cholangitis. However, other causes such as underlying IBD or upper gastrointestinal disorders should also be

considered. The best way to objectively measure symptoms that can be utilized in a clinical trial is through a patient reported outcome measure (PROM). The Simple Cholestatic Complaints Score is a validated PROM in the Netherlands that utilizes pruritus, fatigue, right upper quadrant abdominal pain, and fever.[18] This score is currently under investigation for validation in other countries such as the United States. Additionally, patient-driven PROMs for individual symptoms are currently being developed by PSC Partners Seeking a Cure. Given the fluctuating nature of alkaline phosphatase in PSC, PROMs are a potential solution in obtaining FDA-approval for a drug that improves patient's overall quality of life.

**Inflammatory Bowel Disease.** The fifth pillar of management of PSC is control of underlying IBD. Often, care for PSC is provided by a transplant hepatologist and the IBD component will be managed separately by a general gastroenterologist or IBD specialist. However, these dual disease manifestations are integrally related, and interdisciplinary care is crucial due to the potential of these diseases to interact with each other. Recent work from the International PSC Registry found that colectomy was associated with decreased risk of liver transplantation or death with the most pronounced effect in patients with proctocolectomy with permanent ileostomy[19] Additionally, active IBD post-liver transplant can increase the rate of graft failure, is an independent risk factor for recurrent PSC, and can lead to worse outcomes.[20] There is not enough evidence to strongly recommend one biologic over another in PSC-IBD. Interestingly, although vedolizumab acts mechanistically on the gut-homing pathophysiology in PSC and is well-suited to treat IBD in PSC patients, it has not been found to benefit liver inflammation.[21] Close monitoring of disease activity and tight control of colonic inflammation is essential.

## Emerging therapies for PSC

There are currently no approved therapies for PSC, however new options are emerging. One molecule under investigation is 24-norurosdeoxycholic acid (norucholic acid), a shortened version of UDCA with one less methyl group, preventing conjugation by taurine or glycine, which allows increased cholehepatic shunting and increased anti-inflammatory and anti-fibrotic effects.[22] Recently, Phase 3 clinical trial results (n=301) for norucholic acid (NCT03872921) achieved the primary endpoint of partial normalization of alkaline phosphatase without worsening of fibrosis by liver biopsy (15.1% versus 4.8%).[23] Furthermore, 25% of participants in the treatment group, versus 10% in the control, improved by 1 stage of fibrosis on follow-up liver biopsy at 96 weeks. [23] Other drugs under investigation fall into major themes including modulating the immune system, gut microbiome (such as with vancomycin and bacteriophages), bile acid circulation (PPAR agonists, IBAT inhibitors), and fibroblast response (anti-fibrotics such as CM-101)[4,24]

## Conclusion

PSC is an autoimmune liver disease that can lead to cirrhosis, recurrent cholangitis, or cholangiocarcinoma and currently has no available disease-modifying treatments. All patients with PSC should be referred to specialized centers where they can be considered for enrollment into clinical trials. There are five pillars that should be considered in PSC disease management: malignancy, infection, fibrosis, symptoms, and inflammatory bowel disease. New therapies are under active investigation for PSC with norucholic acid the closest to approval in Europe. PSC is one of the greatest unmet needs in gastroenterology and hepatology that will need much more work done in the years ahead to improve patient care and outcomes.

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# Mirikizumab shows promise in children with ulcerative colitis

In the realm of safety, no deaths occurred, and only three serious adverse events were reported.

By Doug Brunk

In the early months of 2020, as pediatric IBD centers across five countries adjusted to the realities of a global pandemic, a quiet but important effort was underway.

## Early data support new option

At 19 sites, clinicians were enrolling a group of children with moderate to severe active ulcerative colitis (UC) who had burned through corticosteroids, immunomodulators, biologics, or JAK inhibitors, often with disappointing durability. Many had already cycled through anti-TNF therapy, a mainstay with well-known limitations in the pediatric setting. It was in this context that SHINE-1 began: a phase 2, open-label, multicenter exploration of a new IL-23p19 inhibitor, mirikizumab, now tested in children aged 2–17 years.

"Currently, anti-TNF agents are the only FDA approved biologic/advanced therapy for children with moderate to severe UC," the study's first author, Jess L. Kaplan, MD, of the Division of Pediatric Gastroenterology and Nutrition at Mass General for Children, Boston, told *GI & Hepatology News*. "While anti-TNF therapy is effective for many children, it is not effective for all children and many children who initially respond will lose response over time. This is the first published clinical trial data on IL-23 inhibitors in children with UC and shows mirikizumab to be safe and effective for this population."

For the trial, published in *The Lancet Gastroenterology & Hepatology*, Dr. Kaplan and colleagues enrolled 26 of 49 children screened. All received weight based IV induction at weeks 0, 4, and 8, followed by subcutaneous maintenance every 4 weeks through week 52. Non-responders at week 12 received a second 12-week induction.

## Trial results

By week 12, nearly 70% of the children achieved clinical response and about 39% were in clinical remission by modified Mayo score. Endoscopic remission — arguably the most reassuring marker for long-term outcomes in UC — was seen in 54% of study participants, while symptomatic remission occurred in 46%. Pediatric Ulcerative Colitis Activity Index results paralleled these findings; 77% responded and 39% achieved remission by week 12.

By week 52, 54% of study participants maintained clinical response, 38.5% remained in clinical remission, and 38.5% were in endoscopic remission. Notably, 38.5% achieved corticosteroid-free remission for at least 12 weeks leading to week 52.

"I was pleasantly surprised at the relatively high modified Mayo score clinical response rate after induction in a treatment refractory population where 65% of patients were previously biologic exposed," Dr. Kaplan said. "I was also surprised by the relatively high rate of sustained response out to week 52 in week 12 responders and by the relatively high endoscopic remission at week 12."

Endoscopic healing improved over time, with histologic-endoscopic mucosal remission rising from a single patient at week 12 to nine patients (34.6%) by week 52.

Jess L. Kaplan, MD

## Safety and limitations

In the realm of safety, no deaths occurred, and only three serious adverse events were reported: non-infective appendicitis, pseudarthrosis, and worsening UC (the latter leading to the single treatment discontinuation). The most common adverse events were benign and familiar: injection-site pain, headache, fever, and viral URIs. No opportunistic infections, malignancies, or thromboembolic events were reported during the study period. Growth parameters improved steadily in participants who weighed 40 kg or less.

The researchers cited the study's small sample size and lack of randomization as key limitations. They explained that including a placebo or direct comparator group was not feasible or ethically appropriate in pediatric inflammatory bowel disease research.

"The results of this study indicate that mirikizumab therapy in pediatric patients with ulcerative colitis resulted in clinical improvement as assessed using multiple disease activity measures," the authors concluded. "Subgroup analyses also suggest that mirikizumab showed efficacy in participants with a history of failed response to previous biological therapies, suggesting its potential as a treatment option in refractory cases."

## Real-world evidence needed

In an accompanying editorial, Stephanie A. Vuijk, Esmée H. Boute, and Lissy de Ridder, PhD, from the Department of Pediatric Gastroenterology at Erasmus Medical Center in Rotterdam, the Netherlands, wrote that they agreed with the researchers' decision not to include a placebo or other comparator arm in the study, citing ethical and feasibility constraints.

"However, assessing whether mirikizumab is more effective and safer than agents such as anti-TNFs or ustekinumab remain important," they noted. "Head-to-head or randomized controlled trials would offer valuable insights but would be difficult to do because there is a relatively small pool of pediatric patients with ulcerative colitis on biologicals from which to select. Real-world data, including safety registries, should be taken into account to gain more information on safety and efficacy and speed up authorization of new drugs."

## Early pediatric planning lauded

Dr. Kaplan expressed his commendation for the study sponsor, Eli Lilly and Company, recognizing their commitment to initiating a pediatric trial program early in the drug development process.

"In this case, the pediatric phase 2 trial was planned and started well before the medication was approved for adults," he said. "This approach helps reduce the substantial time lag between adult and pediatric approval for novel therapies." He added that larger studies are needed to confirm the safety and efficacy findings from this phase 2 trial, and that a phase 3 trial is currently underway.

*Dr. Kaplan disclosed having received royalties from UpToDate and many of his coauthors disclosed having received consulting fees, research grants, and/or other support from pharmaceutical companies. Vuijk reported grants from KNAW Ter Meulen Beurs 2025; Boute, reported grants from Stichting Sophia Kinderziekenhuis Fonds and the KICC Registry; and de Ridder reported grants from Pifzer and Pfizer Medtalk.*

## Key clinical takeaways

SHINE-1 is the first published trial showing that IL-23p19 inhibition with mirikizumab is safe and effective in children with UC.

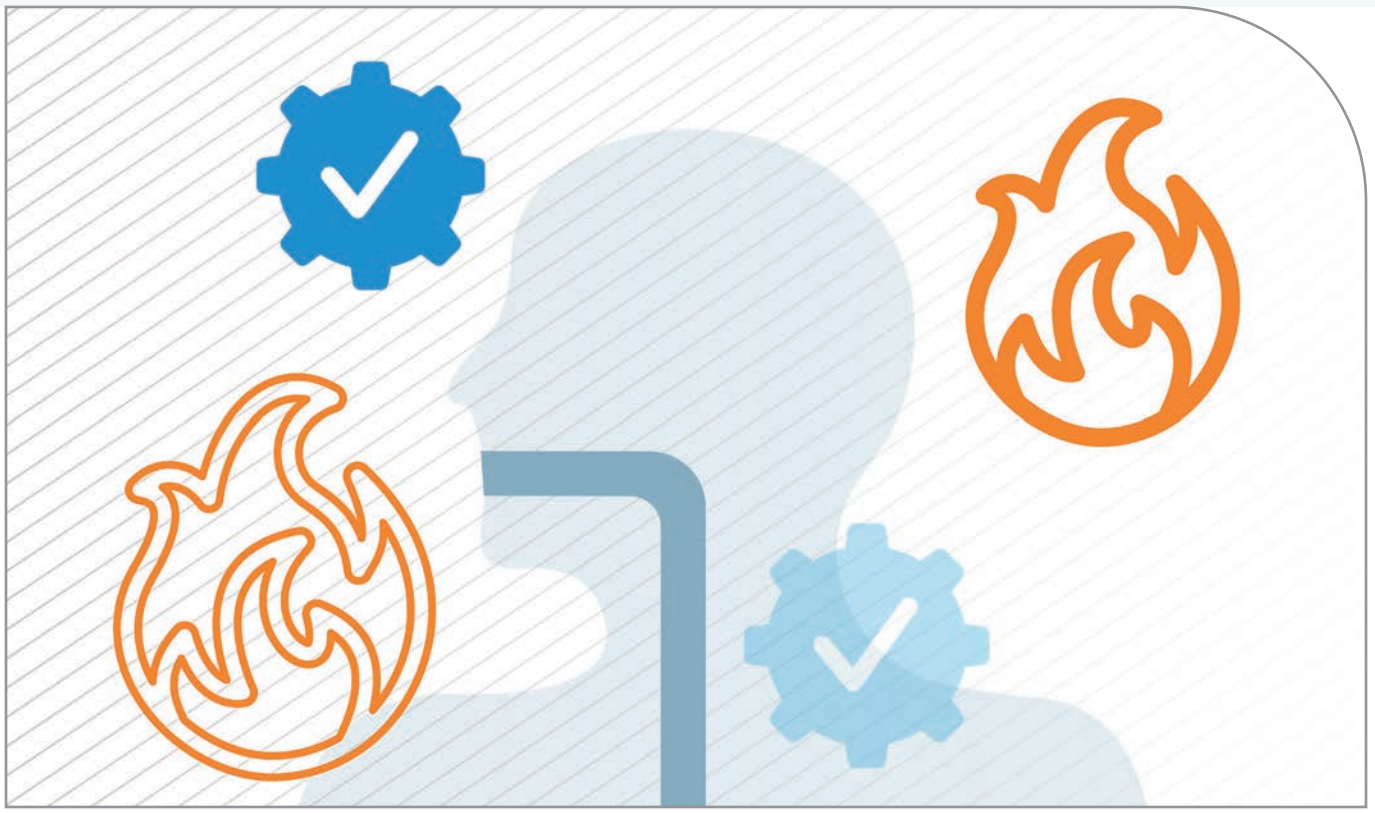
Nearly 70% of children achieved clinical response and more than half achieved endoscopic remission by week 12, despite high prior biologic exposure.

Responses were sustained through 52 weeks, with around 40% achieving clinical, endoscopic, and corticosteroid-free remission.

# Index of Severity for Eosinophilic Esophagitis: Growing body of evidence supports use

I-SEE aims to provide a more comprehensive assessment that goes beyond eosinophil counts to include symptom frequency, complications, and signs of remodeling.

By Andrew Dickerson, MD, Tesuo Shoda, MD, Corey Ketchem, MD, and Carey Cotton, MD



## Introduction

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disease characterized by esophageal dysfunction. However, assessing its severity in clinical practice has historically been variable and subjective, potentially impacting treatment decisions. To standardize this assessment, AGA facilitated the development of the Index of Severity for Eosinophilic Esophagitis (I-SEE).[1] The practical tool integrates key clinicopathologic features from three domains (symptoms and complications, inflammatory features, and fibrostenotic features) into a single score that categorizes disease activity as inactive, mild, moderate, or severe. I-SEE aims to provide a more comprehensive assessment that goes beyond eosinophil counts to include symptom frequency, complications, and signs of remodeling. Since the assessment creation, a growing body of evidence has explored its clinical utility. Highlighted below are several of the key studies examining the application and validity of I-SEE in characterizing EoE patients and assessing treatment response.

## I-SEE in adults

To understand how I-SEE performs in clinical practice, initial validation efforts focused on characterizing its performance in adult populations from clinical trial and real-world settings. A post-hoc analysis of a randomized comparative trial of topical corticosteroids in adults was one of the first studies to apply I-SEE retrospectively.[2] In this cohort, where the majority of individuals were classified as moderate or severe, every subcategory of the score decreased with treatment. Most participants shifted to a lower I-SEE category after treatment. The mean severity score decreased significantly after 8 weeks of therapy, with larger decreases observed in histologic responders (<15 eos/hpf) compared to non-responders. Furthermore, higher baseline I-SEE scores correlated with features not explicitly included in the index, such as lower body mass index, longer duration of dysphagia symptoms prior to diagnosis, and smaller esophageal diameter, supporting its construct validity. Baseline severity also predicted the need for esophageal dilation at the post-treatment endoscopy.

Subsequent real-world data provided further context. A large multi-center observational study assessed physician-perceived disease severity and calculated an adapted I-SEE score.[3] In this real world cohort, only 29% of patients were classified as moderate or severe in the I-SEE category, highlighting differences between trial and real-world populations. The distribution of disease severity was similar between children and adults; however, physicians consistently overestimated severity compared with the I-SEE score, suggesting that use of I-SEE may reduce subjectivity in EoE disease assessment.

To reduce challenges associated with point-of-care use, the AGA developed an I-SEE mobile application.[4] Usability testing across adult and pediatric gastroenterologists and allergists found the app to be user-friendly. Collectively, these descriptive analyses show that the I-SEE score behaves as expected: it decreases both numerically

and categorically with treatment and demonstrates similar severity distributions between children and adults.

## I-SEE in pediatrics

Evaluating how I-SEE generalizes to the pediatric population is important to ensure its applicability and reliability. Recent work applying I-SEE to pediatric cohorts revealed both similarities and important age-related differences. Two retrospective pediatric studies evaluated changes in I-SEE at baseline and over time. A European, multi-center study found that most patients present with a moderate baseline I-SEE score (61%), while only 2% of patients have a severe baseline I-SEE score.[5] Severity in this study was influenced by the use of combination therapy and esophageal perforation; the presence of malnutrition was not reported.

In comparison, a single center US study found a more even distribution of mild (43%), moderate (36%), and severe (21%) I-SEE categories at baseline with severe I-SEE driven by presence of malnourishment (low BMI percentile) and poor feeding.[6] This difference in nutritional status may be explained by a difference in mean age (11 years old in the European cohort versus about 5 years old in the US cohort).

In both studies, food impaction represented a minority of initial presentation (17% in the European cohort and 10% in the US cohort). Esophageal strictures were not a frequent complication (4% of the European cohort at baseline and 1% of the US), which may also contribute to lower I-SEE scores. I-SEE improved in both studies domains over time with treatment. Notably, the European study found that a higher I-SEE score was associated with treatment challenges (i.e. combination therapy). The studies emphasize the utility of I-SEE in pediatric populations for standardizing disease assessment but also highlight the challenges of applying a single, unified score across adults and children. Further high-quality studies in pediatric populations are needed to refine and validate its use in this age group.

## I-SEE and treatment response

Beyond its correlation with traditional disease metrics, determining whether I-SEE can predict treatment response may offer additional value, given that it integrates multiple aspects of disease. This is increasingly important as therapeutic options for EoE expand. Evaluation of the association between I-SEE and topical corticosteroid response has shown that most patients are classified as mild to moderate pre-treatment, while histologic response is lowest in the severe category.[7] Similarly, baseline I-SEE severity is inversely associated with post-treatment symptom response, endoscopic severity, and reduced need for dilation. A comparable pattern was seen with dupilumab, as patients with severe baseline I-SEE scores had lower post-treatment response rates than those with mild or moderate disease.[8]

Furthermore, each 1-unit increase in pre-treatment I-SEE was associated with a 1.5% decrease in histologic response to dupilumab at the <15 eosinophils per high-power field (eos/hpf) cutoff and a 3% decrease at the ≤6 eos/hpf cutoff. Although I-SEE has not been evaluated across all treatment modalities, current evidence suggests it may help stratify likelihood of treatment response by baseline I-SEE severity and provide a more objective measure of change before and after therapy. Severe baseline disease may benefit from more intensive upfront treatment, though additional studies are needed to evaluate I-SEE across different patient population and treatment strategies.

## Molecular correlates of I-SEE

Complementing clinical observations, research has explored the relationship between I-SEE scores and the underlying molecular pathophysiology of EoE. A multi-center study correlated I-SEE scores with the EoE Diagnostic Panel (EDP), a gene expression measure.[9] Total I-SEE score showed a modest inverse correlation with EDP score, indicating that higher clinical severity was associated with higher molecular severity. This was driven mainly by the inflammatory and fibrostenotic domains; the symptoms/complications domain did not correlate with EDP scores. Molecular severity worsened progressively from inactive to moderate I-SEE categories. However, the severe I-SEE group had less severe molecular profiles than the moderate group, possibly because severe scores are often driven by historical complications or fibrosis. Longitudinally, changes in a modified I-SEE score (excluding complications) reflected changes in molecular activity, particularly in the inflammatory and fibrostenotic domains. This suggests that the multidimensional I-SEE captures biologically relevant tissue inflammation and remodeling.

## Conclusions and future directions

The development of I-SEE represents a positive step towards standardizing the assessment of EoE severity. As highlighted in the studies, I-SEE correlates with key clinical features in both adults and children, tracks with treatment response, and inflammatory and fibrostenotic domains reflect molecular disease activity. Although the drivers of severity may differ by age, I-SEE also shows potential for predicting treatment response at follow-up, with higher baseline severity appearing linked to lower response rates.

While this initial evidence is promising, several key areas for future research remain. Prospective or robust real-world validation in diverse EoE populations is crucial to confirm its performance and usability. A major long-term goal is to link specific severity levels to evidence-based treatment and monitoring recommendations, similar to guidelines for other allergic and gastrointestinal diseases. Refining the index may also be necessary, potentially by optimizing symptom assessment, clarifying scoring nuances between children and adults, and incorporating additional metrics. Further research items include correlating I-SEE with EoE endotypes, functional measures such as functional lumen imaging probe, and real-world clinical implementation will help define its validity and practical utility. Optimizing I-SEE through these efforts can enhance communication, strengthen clinical trial design, and support more tailored care for patients.

*Dr. Dickerson is on the speaker's bureau for Takeda and Sanofi/Regeneron. Dr. Shoda had no conflicts to disclose. Dr. Ketchem is on the advisory board of Sanofi. Dr. Cotton is a consultant for Regeneron.*

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# Challenges, opportunities in building more effective community-based IBD care


"I fear practices will lose their relevance if they do not start building systems and processes for cognitive care pathways like IBD."

By Doug Brunk

Most patients with inflammatory bowel disease (IBD) in the United States receive care in community practices that vary widely in size, staffing, and resources. Yet IBD management is becoming increasingly complex, driven by rising prevalence, an aging population, and rapidly evolving therapies.

In a *Gastroenterology* commentary, Erica R. Cohen, MD, of Capital Digestive Care in Chevy Chase, Maryland, and Timothy Ritter, MD, of the GI Alliance in Southlake, Texas, introduced the IBD Community Care Initiative, an AGA-sponsored effort to better understand the realities of IBD management in community settings.

"I fear practices will lose their relevance if they do not start building systems and processes for cognitive care pathways like IBD,"Dr. Cohen, who co-chaired the initiative with Dr. Ritter, told *GI & Hepatology News*. "All of this risks negatively impacting patient care. To me, all of this is very urgent."

In May 2024, Drs. Cohen and Ritter worked with the IBD Community Care Initiative Working Group to survey 102 clinicians from private practices with at least 10 providers and a weekly IBD caseload of 10 or more patients. The survey focused on how integrated care models can be implemented outside academic centers. Respondents highlighted four challenges familiar to many gastroenterologists:

- Ensuring fair compensation for complex, primarily cognitive work
- Preventing delays in care and care coordination and access
- Lack of an identified care team
- Limited experience implementing new care models in private practice

Despite these barriers, the working group identified several integrated care models already operating successfully in community settings.

## Remote monitoring

Third-party remote monitoring platforms allow practices to track symptoms between visits, receive alerts when deterioration occurs, and intervene early. These models typically rely on risk-based payer contracts or remote patient monitoring reimbursement codes but require minimal upfront investment, making them appealing to small and mid-sized practices. They also promote proactive rather than reactive care and have demonstrated reductions in hospital utilization.

## Advanced practice provider–led programs

Another option is the development of APP-led programs in which nurse practitioners or physician assistants coordinate triage, patient education, and routine follow-up using structured protocols. Such programs expand patient access and distribute workload more evenly, allowing physicians to focus on the most complex decisions. Many practices adopting this model report improved satisfaction among both clinicians and patients.

## Hospital partnerships

Some community groups have partnered with local hospitals through joint ventures to gain access to nutritionists, social workers, patient navigators, and other services that are difficult for private practices to support independently. By sharing resources and aligning incentives, practices can build multidisciplinary teams without absorbing all labor costs, while hospitals benefit from increased downstream referrals.

## Chronic care models (CCMs)

CCMs offer another pathway by enabling practices to bill for non–face-to-face management activities. Practices that implement CCM typically assign oversight to a physician-APP team and build structured processes for regular patient contact, symptom monitoring, and coordination. The reimbursement generated can support hiring a triage nurse, pharmacy technician, or part-time dietitian — roles that help lighten clinician workload and accelerate time-sensitive care.

## IBD service lines

Several larger community groups have created dedicated IBD service lines — essentially an IBD "center within a center" — with physicians, dietitians, behavioral health specialists, and navigators integrated into a single pathway. These models most closely resemble academic IBD centers and offer clear benefits for patient outcomes and practice growth, though they require substantial investment and cultural alignment.

To help practices operationalize integrated IBD care, the working group outlined a four-step approach:

1. **Assess current workflows and resources.** Practices should map out their processes, staffing, and existing gaps.
2. **Conduct a structured gap analysis.** This can reveal unmet internal needs and opportunities in the local market, such as favorable value-based contracts or potential hospital collaborators.
3. **Evaluate potential care models.** Practices should consider which options best match their size, staffing, electronic infrastructure, and payer mix.
4. **Secure organizational buy-in.** Leaders must present a clear and

Dr. Cohen discussed the importance of the IBD Community Care Initiative in an interview with *GI & Hepatology News.*

**Your survey of 102 community providers identified four major barriers to integrated IBD care — compensation, access, lack of multidisciplinary resources, and operational inexperience. Which of these barriers did you find most surprising or most urgent, and why?**

**Dr. Cohen:** I graduated from the Cedars-Sinai IBD fellowship and decided to pursue a career in my hometown community. I realized very soon in the clinical trenches that these are very real barriers, so none of them are surprising to me. I have seen these challenges lead to subspecialty-trained physicians avoiding cognitive care management in favor of procedural-based practices.

I am lucky that Capital Digestive Care values cognitive care delivery and allowed me to explore solutions to many of these challenges. In this quest, I realized there are many IBD-focused community providers across the country who are light years ahead of me in answering these questions. I asked Dr. Ritter, who had been mentoring me on setting up my own clinic, if he would co-chair the AGA IBD Community Care Initiative so we could systematically identify the challenges, explore solutions already in practice around the country, and create space to continue this conversation.

**The initiative outlines several community-ready care models — APP-led programs, chronic care models, third-party platforms, joint ventures, and IBD service lines. Based on your workshop discussions, which model do you believe is most feasible for an average mid-sized community GI practice to adopt first, and what early wins can they expect?**

**Dr. Cohen:** This depends on the practice culture, available financial support, local hospital interest, and identification of provider champions. Using a third-party platform may be the easiest to implement because there is no upfront financial cost or resource requirement. If the platform utilizes risk-based contracting or chronic care reimbursement, the practice should see a financial upside relatively quickly, and there are data showing that these programs can decrease acute care utilization and improve quality of life. These platforms can reach a larger volume of patients than an APP-led program or a chronic care model but run the risk of lack of oversight from the practice, additional administrative burden, and further limiting the scope of gastroenterology practice.

**Many providers cite poor compensation for cognitive, complex care as a core obstacle. What strategies — such as hybrid RVU/salary models or stipends tied to cognitive-care responsibilities — do you think have the greatest potential to gain traction in community practices? What makes these approaches realistic?**

**Dr. Cohen:** I was very surprised to find during this workshop how many practices already follow an equal-shares model. I think this is wonderful but very hard to change culturally, as it requires all partners to agree that compensation models should be realigned. The most realistic approach is to create stipends for IBD Program Directors with defined expectations and deliverables that benefit both the physician and the practice. Financial support can be drawn from CCM billing, clinical research participation, community marketing, provider education, or oversight of infusion services/prior authorization.

**Your data show that only 6% of community practices have a formal urgent-care process for IBD, despite widespread agreement on its importance. What are the simplest, most immediately implementable steps practices can take to improve same-day access and reduce ED visits?**

**Dr. Cohen:** Small changes can lead to improved access for patients and less manual work for clinicians.

- Educate patients on what symptoms are defined as urgent. The Quorus urgent-care toolkit has handouts that practices can provide to patients through email blasts or at clinic visits.
- Have an urgent phone line (can be managed by a secretary, infusion MA, or prior authorization staff) that uses a templated form to determine the urgency of the visit and sends it to a team member.
- Have one APP urgent-slot patient visit open per day.

These small changes create a team-based system approach to addressing urgent concerns.

**Many community practices lack dietitians, behavioral health specialists, and trained navigators. You propose a "Physician/APP co-champion" model. What qualities make for an effective co-champion, and how can practices identify or cultivate them when resources are limited?**

**Dr. Cohen:** Effective co-champions are clinicians who are interested in focusing their practice on IBD management. The upfront time required to set up these internal processes will benefit clinicians in the future by reducing clerical and administrative burdens and allowing them to focus on direct patient care.

**To best operationalize integrated care, you outline four steps — assessment, gap analysis, model selection, and presenting a case. From your experience, which of these steps tends to derail practices most often, and what guidance would you offer to help leaders keep momentum during implementation?**

**Dr. Cohen:** It is atypical for practice leadership to consider cognitive-care clinical pathway development for IBD. There are community practices whose leadership has successfully implemented IBD care models, but only a minority of panel members worked in this type of system. Most commonly, these models were developed from the ground up by motivated clinicians who wanted a sustainable practice. From a clinician perspective, building these care models can seem daunting, as we were never taught how to create a business model and pitch. Through this initiative, we hope to lay the groundwork for more widespread utilization.

Erica R. Cohen, MD

compelling case that integrated care improves patient outcomes, enhances staff satisfaction, and generates new revenue streams while supporting broader practice goals.

According to Ritter, each practice "needs to continually reassess how successful their model is and be open to revising the model as their practice and healthcare policies and economics change over time," he said.

Cohen characterized the initiative as "a wonderful first step in starting this important conversation," she said. "Future directions include career mentorship for fellows and early-career physicians, formalized advocacy to payers, implementation of intestinal ultrasound, and data collection on clinical outcomes, financial viability, and qualitative measures in these models."

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# 2025 Sherman Prize Recipient Dr. Oriana Damas advances equity and innovation in IBD care

**As a national leader in Hispanic IBD research, Dr. Damas bridges discovery and patient care to deliver more inclusive, precision-driven treatment.**

By Sierra Rendon

*"What we've discovered has been transformative... environmental factors matter more than genetics in determining when IBD presents in this population."*

Oriana M. Damas, MD, MSCTI, embodies the physician-scientist model at the heart of modern gastroenterology — integrating rigorous research, compassionate clinical care, and a deep commitment to equity in inflammatory bowel disease (IBD). An associate professor of medicine in the Division of Digestive Health and Liver Diseases at the University of Miami Miller School of Medicine, Dr. Damas currently serves as interim director of the Crohn's and Colitis Center and Director of Translational Studies, where she leads efforts to bring discovery directly to patient care.

A Miami native, Dr. Damas completed her medical degree, internal medicine residency, and gastroenterology fellowship at the University of Miami. During fellowship, she pursued a dedicated research track focused on IBD genetics, supported by a UCB and IBD Working Group Fellowship grant, and was elected Chief Fellow for her clinical excellence and leadership. Mentored by Dr. Maria Abreu, she quickly recognized a critical gap in understanding IBD among Hispanic and Spanish-speaking populations in South Florida — an insight that shaped her career.

Dr. Damas has since become a national leader in defining the epidemiology, phenotype, and genetic risk factors of IBD in Hispanic patients, including pivotal work demonstrating the relevance of NUDT15 testing in this population. Her current NIH-funded research explores diet and metabolic health as therapeutic strategies, including a culturally tailored anti-inflammatory South Florida diet for ulcerative colitis. Her work has been recognized with numerous honors, including the 2025 Sherman Emerging Leader Prize, reflecting a career driven not only by discovery, but by service, mentorship, and trust.

**Congratulations on receiving the Sherman Prize. What does this recognition mean to you at this stage of your career?**

**Dr. Damas:** It means the world to me. I think the Sherman Prize is the most important recognition you can receive as an IBD physician, and it is the biggest honor of my career. This award validates the work we're doing — not just in the lab or clinic, but in asking the difficult questions about why our Hispanic and Latino patients experience IBD differently, why diet matters so much, but we haven't been able to precisely define how, and how we can move toward truly personalized IBD care. At this point in my career, as I'm building our research programs and mentoring the next generation, this recognition reinforces that we're on the right path. It energizes me to keep pushing forward with our work on environmental determinants, dietary interventions, and ensuring that underserved populations are included in IBD research. This isn't just about my accomplishments; it's about the team, the patients who trust us with their care and participation in our studies, and the critical work that still needs to be done.

**Your work has been instrumental in helping define IBD in Hispanic immigrant populations. What first led you to focus your research on this community, and what are the most important insights you've uncovered so far?**

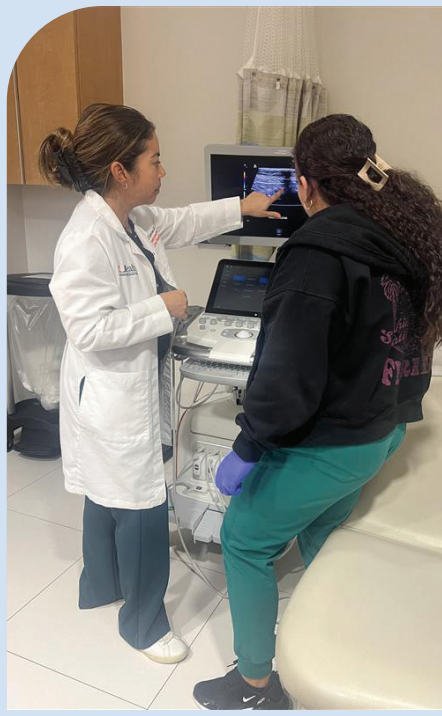
**Dr. Damas:** I noticed early in my career that we were seeing numerous Hispanic patients with IBD in our clinic, but there was virtually no data describing their disease phenotype or outcomes. Together with my mentors, I decided to create a registry that has now become one of the largest databases of Hispanic patients with IBD in the U.S.

What we've discovered has been transformative. Our environmental and genetic studies revealed that environmental factors matter more than genetics in determining when IBD presents in this population. We found that duration of exposure to a Western environment is a critical factor for age of IBD diagnosis — we've examined this across patients in Colombia, foreign-born patients in the U.S., and U.S.-born patients of Hispanic heritage. Remarkably, within just one generation of being U.S.-born, the disease phenotype becomes similar to other U.S.-born patients, demonstrating how powerfully environmental factors shape IBD risk and presentation.

We've also made important pharmacogenomic discoveries — our work showed that the NUDT15 variant is crucial to check in Hispanic patients because it significantly increases leukopenia risk with thiopurine therapy. And through detailed dietary analyses, we've identified specific foods in traditional Hispanic diets that are associated with better outcomes for patients with IBD.

All of these discoveries have led us to dig deeper into environmental determinants and to develop several pivotal dietary intervention trials, including a large clinical trial for UC patients. I genuinely believe this work will change outcomes for Hispanic patients and for all patients with IBD broadly, because understanding how environment and diet modify disease gives us powerful tools for personalized, precision medicine approaches that can benefit everyone.

Left: Dr. Damas working in her practice
Right: She and her family in Belguim.



**Much of your recent research explores the interplay between genetic and environmental risk factors — especially diet — in IBD. What emerging patterns or hypotheses are you most excited about?**

**Dr. Damas:** I am most excited about personalizing diets based on genetics and microbiome composition — that is the future of IBD care. We have already identified key genetic variants that shape how nutrients influence inflammation. We plan to study these interactions in animal models and in a human clinical trial. Our current clinical trials also collect genetic and stool microbiome samples, which will help us learn how to personalize dietary interventions for individual patients.

**How do you currently see the landscape of IBD care evolving for underrepresented or immigrant communities, and where do you believe the biggest gaps still exist?**

**Dr. Damas:** The biggest issue is access to care, and that will only worsen in the coming years as many people lose medical coverage in the U.S. This will broadly affect everyone, but I suspect it will disproportionately impact underrepresented minorities, especially immigrants. That deeply concerns me. As physicians, we have to advocate for our patients. I encourage everyone to get involved with foundations and advocacy efforts because this is where I see the greatest challenge in the foreseeable future.

Beyond policy and access to care, another critical issue is patient education and IBD-related counseling.We need to do a better job teaching our patients everything related to their care — from disease prognosis to medication monitoring to health maintenance. This gap is magnified in minority populations, especially those facing English language barriers.

**How did your experience with the AGA FORWARD program influence your professional trajectory or leadership approach?**

**Dr. Damas:** The experience taught me critical leadership skills and grantsmanship, but most importantly, I found a community of talented researchers and physicians who look like me and share the same drive to pursue excellence in patient care. That sense of community is incredibly special, and the bonds you form are priceless.

**What advances in IBD research or clinical practice do you believe will have the greatest impact in the coming years?**

**Dr. Damas:** I believe prevention will be one of the most transformative areas in IBD over the next 10 years. We're finally understanding the environmental determinants that trigger IBD, and this knowledge points to modifiable risk factors we can actually intervene on. For example, our work is showing how Western environmental exposure accelerates IBD onset in immigrant populations — with U.S.-born Colombians diagnosed 14 years earlier than Colombian-born counterparts — demonstrates that environment matters more than genetics. Within one generation, the disease phenotype shifts completely. This tells us there's a critical window where we could potentially delay or even prevent IBD onset in high-risk individuals. Early and childhood exposures are key; we see this over and over, including in our own diverse cohort. If we can identify these high-risk populations early and modify their environmental exposures early, we could fundamentally change the trajectory of this disease.

Personalized nutrition is on the horizon, though it's still in its early stages in IBD. Our group and other study groups are trying to understand how individual genetics and microbiome composition determine which foods help or harm specific patients. We've already identified key genetic variants that shape how nutrients influence inflammation, but we would like more validation of these findings and to test this in a rigorous clinical trial. I'm confident that soon, we'll be able to increasingly offer patients personalized dietary prescriptions based on their genetic and microbiome profiles. This isn't just about managing symptoms — it's about using diet as precision medicine to modify disease course and improve long-term outcomes for all IBD patients

**As someone deeply invested in both scientific discovery and patient-centered care, how do you balance research, clinical duties, and mentorship at the University of Miami?**

**Dr. Damas:** As best I can! And by focusing on one item at a time. I've learned there is no such thing as multitasking if you want to do things right. Each item requires focus. Some more than others. Every week, the priorities change, and I always try to tackle at least once those non-urgent but essential things that keep me happy in my career (e.g. research or mentoring)

**What advice would you give to early-career gastroenterologists — especially those interested in health disparities research or immigrant health?**

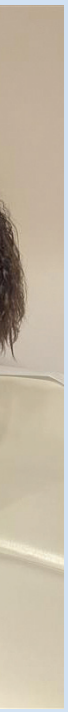
**Dr. Damas:** Find the area that interests you most and where you want to make a difference. Couple that with identifying research priorities and areas of unmet need. Together, that's the secret sauce: need + what you're good at + what you love.

**On a personal note, what keeps you motivated outside the lab and clinic? Are there hobbies or routines that help you recharge?**

**Dr. Damas:** Yes, for me it's about balancing career demands with family life. When I can make it to my kid's game or cook a great dinner — normal mom and family life things — I feel complete and recharged. The occasional spa massage also helps. I also love to travel and spend time thinking about the next place we will be going. I like to plan the whole thing myself.

**What advances in IBD research or clinical practice do you believe will have the greatest impact in the coming years?**

**Dr. Damas:** Based on our team's work, there are differences in genetic risk among Hispanic patients compared to non-Hispanic Whites. We do not know whether these differences in genetic risk translate into differences in response to medical therapy (due to the genetic mechanisms that led to the development of the medications). Our next step is to determine whether this is important.



## Lightning round

**Tell us about a mentor and what you learned from them?**

Maria Abreu, MD. She taught me that you have to do research you love — that passion transforms the work.

**What are you excited about working on right now?**

I'm currently working on many, many projects, and they all excite me in their own way! Diet clinical trials, gene-diet interactions, environmental factors contributing to IBD in Latin America, and the list goes on!

**Best piece of advice you've given or received?**

If you are upset about something, don't react immediately. Take time, let emotions cool, and act the next day.

**What's your secret talent?**

I bring energy and passion to the things I love doing.

**What is your favorite GI organ and why?**

The ileum! Also, it's not an organ, but I love the villi and how beautiful it looks when you get in.

**Favorite AGA memory?**

The 2024 Southeast Florida Women in GI's Conference, of course.

**If you could have dinner with anyone, who would it be and why?**

It would be with Shakira and with Carlos Vives because they are my favorite singers.

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