

GI&Hepatology News

American Gastroenterological Association's official newspaper
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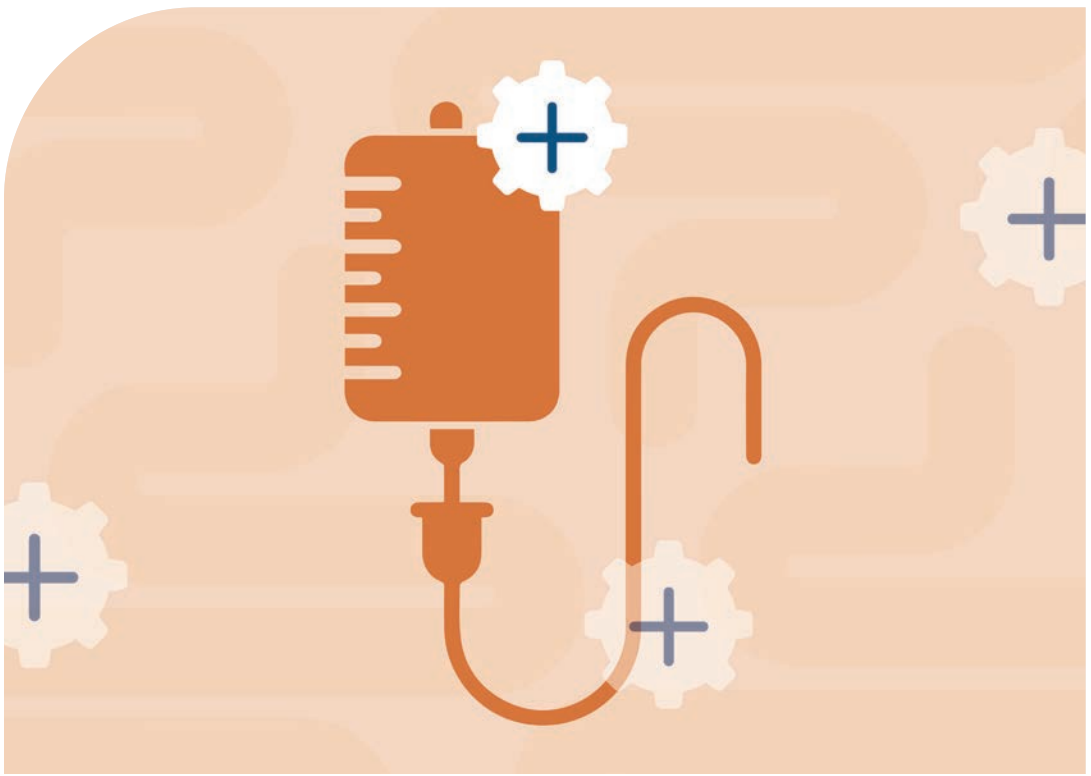

# Adding upadacitinib to vedolizumab may double endoscopic remission rates in UC

Combination induction for eight weeks outperformed vedolizumab alone in a multicenter randomized trial.

By Jess Allerton

A multicenter randomized trial published in *Clinical Gastroenterology and Hepatology* has found that combining upadacitinib with vedolizumab for eight weeks led to significantly higher rates of endoscopic and clinical remission in patients with moderate-to-severe ulcerative colitis (UC) than vedolizumab alone.

The study explored whether using two advanced therapies together at the start of treatment could improve induction outcomes.

Despite the growing number of treatment options for UC, many patients fail to achieve endoscopic remission during induction therapy, prompting continued interest in more effective approaches.

Researchers enrolled 113 adults with moderate-to-severe UC across eight centers in China. Participants received either vedolizumab alone or vedolizumab combined with upadacitinib for eight weeks. The primary endpoint was endoscopic remission, defined as complete resolution of visible inflammation on colonoscopy.

Continues • Page 10

## Delphi panel backs liver stiffness measures for monitoring MASH therapy

"Quantitative, simple, reliable, and widely available tools in clinical practice are urgently needed." As MASH therapies expand, liver stiffness measurement may provide a practical way to monitor response while reducing reliance on invasive, costly serial biopsies.

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## Study supports repeat colonoscopy after positive interval FIT following colonoscopy

"Patients who have a positive fecal immunochemical test (FIT) after a colonoscopy and before they are next due for colon screening are at higher risk of colorectal cancer when compared to patients who have an interval negative FIT or do not have FIT performed."

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# SHIFT WHEN YOU SWITCH

## TO RINVOQ

**For TNFi-IR patients or if a TNFi is clinically inadvisable**

**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.**

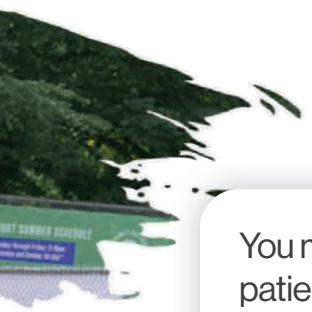
For adults with moderate to severe Crohn's disease (CD) or ulcerative colitis (UC) after inadequate response to a TNFi or another approved systemic therapy if a TNFi is clinically inadvisable[1]

# 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. 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

IR=intolerance or inadequate response; 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; hypoglycemia in patients with diabetes; 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.

## HYPOGLYCEMIA IN PATIENTS WITH DIABETES

Hypoglycemia, including severe hypoglycemia, has been reported following initiation of RINVOQ and other JAK inhibitors in patients with diabetes. During treatment with RINVOQ, consider increased monitoring of blood glucose as clinically indicated in patients with diabetes. Advise patients with diabetes to notify their healthcare provider if they develop signs or symptoms of hypoglycemia.

## 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.

### Hypoglycemia in Patients with Diabetes

Hypoglycemia, including severe hypoglycemia, has been reported following initiation of RINVOQ/RINVOQ LQ and other JAK inhibitors in patients with diabetes. During treatment with RINVOQ/RINVOQ LQ, consider increased monitoring of blood glucose as clinically indicated in patients with diabetes. Advise patients with diabetes to notify their healthcare provider if they develop signs or symptoms of hypoglycemia.

### 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]*
- Hypoglycemia in Patients with Diabetes *[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.

**Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of RINVOQ/RINVOQ LQ. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

*Metabolism and nutrition disorders:* Hypoglycemia

**DRUG INTERACTIONS**

**Strong CYP3A4 Inhibitors**

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

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

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

**Strong CYP3A4 Inducers**

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

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

Pregnancy Surveillance Program

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

Risk Summary

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

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

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

Clinical Considerations

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

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

Data

*Animal Data*

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

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

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

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

**Lactation**

Risk Summary

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

Data

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

**Females and Males of Reproductive Potential**

Pregnancy Testing

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

Contraception

*Females*

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

**Pediatric Use**

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

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

**Geriatric Use**

Ulcerative Colitis

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

Crohn's Disease

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

**Renal Impairment**

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

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

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

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

**Hepatic Impairment**

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

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

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

**CLINICAL PHARMACOLOGY**

**Pharmacokinetics**

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

## NONCLINICAL TOXICOLOGY

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

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

Impairment of Fertility

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

## PATIENT COUNSELING INFORMATION

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

Serious Infections

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

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

Malignancies

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

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

Major Adverse Cardiovascular Events

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

Thrombosis

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

Hypersensitivity Reactions

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

Gastrointestinal Perforations

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

Hypoglycemia in Patients with Diabetes

Consider advising patients with diabetes to increase monitoring of blood glucose since hypoglycemia, including severe hypoglycemia, has been reported after starting RINVOQ/RINVOQ LQ. Advise patients with diabetes to notify their healthcare provider if they develop signs or symptoms of hypoglycemia *[see Warnings and Precautions]*.

Retinal Detachment

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

Laboratory Abnormalities

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

Vaccinations

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

Embryo-Fetal Toxicity

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

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

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

Lactation

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

Administration

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

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

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

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

Medication Residue in Stool

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

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# GI care in a hybrid world

Virtual visits have earned a place in GI practice. Building hybrid care that works means matching the tool to the moment.

Telehealth, particularly virtual visits, has become an established part of many GI practices. Its role continues to evolve, and the central question now is not simply whether it "works," but how to use it well: where it adds value, where it falls short, and how it should be integrated into clinical care.

In gastroenterology, the answer is practical — and opinions vary. Some clinicians are comfortable seeing carefully selected new patients virtually, especially when records, laboratory data, imaging, and the referral question are available in advance. Others prefer that new consultations occur in person and reserve telehealth for established patients, medication follow-up, counseling, results review, or chronic disease monitoring. These differences reflect legitimate concerns about diagnostic confidence, rapport, the physical examination, workflow, medicolegal considerations, and the ability to move quickly to a different level of care when needed. Patient preferences are just as varied. Some patients strongly prefer telehealth because it reduces travel, time away from work, childcare challenges, and the burden of frequent visits. Others feel that a virtual visit is not an adequate substitute for being seen in person, particularly when symptoms are new, complex, or worrisome. All these perspectives are valid and should inform how we design hybrid care.

The challenge is to use telehealth without overextending it. Virtual visits can support triage, counseling, and follow-up, but they should not become a substitute when examination, testing, endoscopy, or urgent evaluation is needed. A successful hybrid model depends on how smoothly a patient can move from a virtual encounter to in-person care when the clinical situation calls for it. That requires more than simply offering video visits. Practices need clear scheduling criteria, thoughtful triage, reliable follow-up systems, language access, and attention to digital literacy. We also need to recognize that telehealth may reduce barriers for some patients while introducing new ones for others. Policy questions around reimbursement, licensure, documentation, and audio-only care will continue to shape how widely and equitably virtual care can be used.

Used well, telehealth can improve access, reduce unnecessary travel, and support more efficient use of the GI workforce. Used poorly, it can fragment care or delay necessary evaluation. As telehealth becomes part of routine practice, its value should be measured not only by convenience, but also by clinical outcomes, quality, equity, and patient experience. Hybrid care will succeed only if we design it with those standards in mind.

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

# The impact of researchers

The AGA Research Foundation helps fund investigators like Sara Di Rienzi, PhD, whose microbiome research may open new paths for understanding and treating GI disease.

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

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Donations to the AGA Research Foundation helped AGA Pilot Research Award Recipient Sara Di Rienzi, PhD, conduct research that will help to advance our understanding of the intestinal microbiome. The interactions between the gut and the body have been recognized for millennia as critical for health. Investigations into the role of the intestinal microbiome on health provide a new way to interrogate these interactions and suggest novel ways to deliver therapeutic control over health from the gut. Such research pursuits, however, are inherently risky both for securing funding and for making career transitions.

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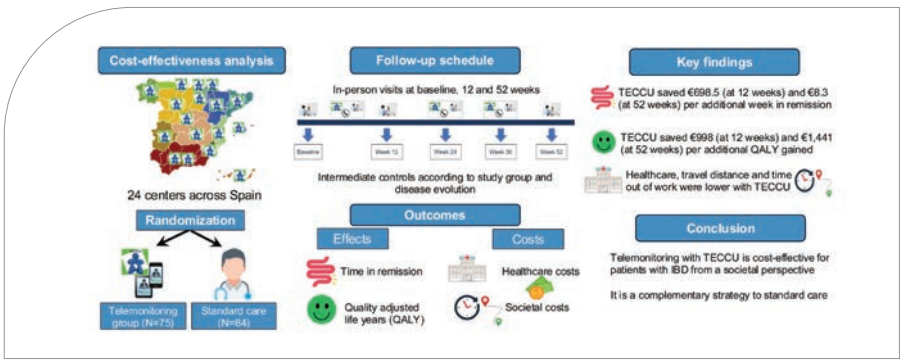
# Remote monitoring matches standard IBD follow-up with fewer office visits, trial finds

In a 24-hospital Spanish randomized trial, patients with active inflammatory bowel disease starting advanced therapy who used a telemonitoring app had disease control noninferior to standard care while making fewer in-person visits.

By Doug Brunk




Graphical abstract courtesy of *Clinical Gastroenterology and Hepatology.*

A telemonitoring program allowed patients with active inflammatory bowel disease (IBD) to shift much of their follow-up out of the clinic without compromising disease control, according to a multicenter randomized trial across Spain published in *Clinical Gastroenterology and Hepatology*.

The trial randomized 159 adults starting immunosuppressants, biologic therapies, or Janus kinase inhibitors at 24 hospitals to use the Telemonitoring of Crohn's Disease and Ulcerative Colitis (TECCU) app (75 patients) or receive standard care (84 patients), with follow-up over one year. The study was powered to test whether telemonitoring was noninferior to standard care for clinical remission.

"This study is important because the evidence on the economic impact of telemonitoring in inflammatory bowel disease is limited," study author Javier Del Hoyo, MD, PhD, of the gastroenterology department at La Fe University and Polytechnic Hospital, Valencia, Spain, told GI & Hepatology News. "However, the efficiency of telemonitoring in terms of cost-effectiveness has been studied in a few centers thus far."

Participants had either Crohn's disease or ulcerative colitis. The primary endpoint was time spent in remission; researchers also assessed quality-adjusted life years (QALYs), a measure combining quality and length of life, and tracked health care use, travel expenses, lost work productivity, and other out-of-pocket patient costs.

After 52 weeks, patients in the TECCU group spent an average of 30.7 weeks in remission, compared with 34.1 weeks in the standard-care group — a difference that did not reach statistical significance. Among patients with Crohn's disease, time in remission was nearly the same in both groups; among patients with ulcerative colitis, the numerical difference favored standard care, though the authors reported that telemonitoring remained noninferior overall. Blood and stool markers of inflammation, including C-reactive protein and fecal calprotectin, improved similarly in both groups, and quality of life improved in both. EuroQol 5-Dimension 5-Level scores rose from 0.82 to 0.87 in the TECCU group and from 0.76 to 0.89 in the standard-care group.

Javier Del Hoyo, MD

The clearest difference was in how care was delivered. Patients in both groups had a similar number of scheduled contacts with their care teams — 6.9 per patient with TECCU versus 7.0 with standard care — but telemonitoring shifted those contacts away from the clinic. TECCU patients averaged 3.1 in-person visits versus 4.8 with standard care, and 3.7 remote contacts versus 2.3.

That shift was associated with lower costs. Average health care spending was 370 euros per patient in the TECCU group versus 406 euros with standard care, with most of the difference coming from fewer in-person visits. Patients using TECCU also traveled less for appointments, averaging 69 km during the study versus 175 km with standard care, with correspondingly lower travel expenses (17 vs 39 euros per patient). TECCU participation was also associated with savings of about 13 hours of work time per patient.

In the cost-utility analysis, telemonitoring was less expensive than standard care in about 74% of simulated scenarios. Using a willingness-to-pay threshold of 20,000 euros per QALY, the authors reported that telemonitoring had a 94% probability of being cost-effective at 12 weeks and a 90% probability at 52 weeks.

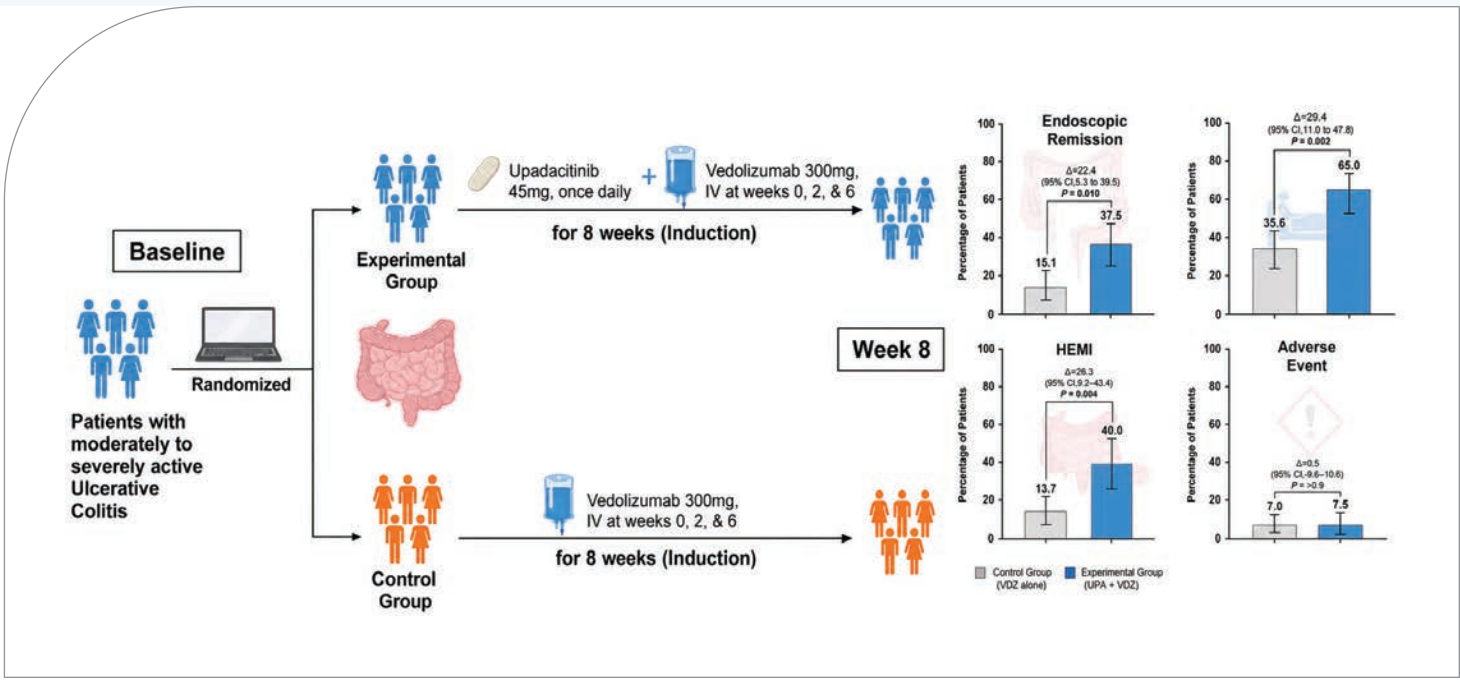
"The results presented in this study can guide decision-makers regarding the implementation of telemonitoring in patients with IBD," Del Hoyo said. "To date, one of the barriers to the widespread use of telemedicine was the lack of economic data, and our work provides evidence that supports telemonitoring as an efficient alternative in this setting. Therefore, these findings provide a rationale for the adoption of telemonitoring as a complement to standard care in patients with active IBD in daily practice."

He and his coauthors acknowledged several limitations. The trial was powered to assess noninferiority for clinical remission, not differences in quality of life, productivity, or economic outcomes. Follow-up was limited to 52 weeks, potentially missing longer-term cost trends. The COVID-19 pandemic may also have influenced health care use patterns and increased remote contacts in the standard-care arm.

"This study is the result of more than 10 years of work," Del Hoyo said. "Our study showed that the cost-effectiveness profile of telemonitoring is similarly beneficial in alternative costing scenarios. This reinforces the reproducibility of the results not only in Spain, but also in other health care systems."

*The study was funded by the Instituto de Salud Carlos III, co-funded by the European Regional Development Fund, and by an investigator-initiated study from Johnson & Johnson. The authors reported no conflicts of interest related to the study.*

# Adding upadacitinib to vedolizumab may double endoscopic remission rates in UC




Graphical abstract courtesy of *Clinical Gastroenterology and Hepatology.*

Continued From Page 1

At week eight, endoscopic remission was achieved by 37.5% of patients receiving combination therapy compared with 15.1% of those receiving vedolizumab alone. Clinical remission rates were also higher in the combination arm (65% vs. 35.6%), as were rates of histologic-endoscopic mucosal improvement.

According to study authors, the findings suggest that adding upadacitinib may help patients achieve deeper remission earlier in the treatment course. Both endoscopic healing and histologic improvement are increasingly recognized as important treatment targets because of their association with improved long-term outcomes.

Safety outcomes were similar between the two groups during the eight-week induction period. Adverse events occurred in fewer than 10% of patients in either arm, and no serious adverse events were reported. One patient receiving combination therapy discontinued treatment because of severe rash and elevated lipid levels.

"The primary takeaway is that combining upadacitinib and vedolizumab for an 8eight-week induction period is highly effective for patients with moderate-to-severe ulcerative colitis," said Jiayin Yao, Associate Chief Physician and corresponding author. "Our trial demonstrated that this combination more than doubled the rate of endoscopic remission compared to vedolizumab monotherapy. It also significantly increased clinical remission rates and histologic-endoscopic mucosal improvement. Importantly, this enhanced efficacy did not come at the cost of short-term safety; adverse event rates were low and comparable between both groups, with no serious adverse events reported during the eight-week period."

"Historically, advanced monotherapies for UC have faced a therapeutic ceiling, with remission rates rarely exceeding 30%," Yao said. "Our findings offer a compelling hit-hard-and-early strategy to break through this ceiling. By pairing a potent, rapid-acting small molecule, upadacitinib, with a gut-selective biologic known for its excellent long-term safety, vedolizumab, we can rapidly induce deep mucosal healing. Because early mucosal healing is associated with a drastic reduction in the long-term risk of colectomy, this combination induction approach provides a promising pathway to optimize early patient outcomes while setting the stage for safe, long-term maintenance therapy."

Several limitations should be considered. The trial was stopped early after an interim analysis demonstrated benefit, resulting in a smaller study population than originally planned. The study was also open-label, and there was no upadacitinib-only arm, making it difficult to determine the specific contribution of combination therapy.

Looking ahead, the investigators emphasized the need for longer-term follow-up. "We are currently continuing the 54-week maintenance phase of this trial, which will provide crucial long-term efficacy and safety data," Yao said. Those findings will help determine whether the benefits observed during induction can be sustained over time and whether the strategy has a role in routine clinical practice.

*The authors reported having no disclosures.*

# Pediatric-onset Crohn's not tied to worse birth outcomes

Disease activity during pregnancy appeared more closely associated with fetal growth than age at Crohn's disease diagnosis.

By Doug Brunk

Women diagnosed with Crohn's disease during childhood or adolescence did not face a higher risk of preterm delivery or adverse neonatal outcomes than women diagnosed in adulthood, according to a retrospective study of 262 births. In some measures of fetal growth, outcomes favored the pediatric-onset group: Infants born to mothers with pediatric-onset Crohn's disease were less likely to be small for gestational age and had higher birth-weight percentiles.

Disease activity during pregnancy, rather than age at diagnosis, emerged as a stronger predictor of neonatal outcomes.

"Despite the pregnancy literature, a key question remains unanswered: How do pregnancy and neonatal outcomes compare in women diagnosed with Crohn's disease in childhood versus adulthood?" said senior author Jacob A. Kurowski, MD, of Cleveland Clinic's Division of Pediatric Gastroenterology, Hepatology and Nutrition in an interview with *GI & Hepatology News*. "Our study set out to answer that question, and the results were reassuring. With much greater certainty, I can now tell young women and their parents that based on our findings, they can expect similar, if not better, outcomes for both themselves and their children."

The study, published in *Gastro Hep Advances*, evaluated pregnancy and neonatal outcomes among women with Crohn's disease who delivered at Cleveland Clinic between 2012 and 2023. Researchers sought to determine whether pediatric-onset disease, which is often associated with greater disease burden and longer cumulative disease duration, affected gestational age at delivery or neonatal birth weight.

Jacob A. Kurowski, MD

The investigators reviewed 262 births among 179 women with Crohn's disease. Of those births, 105 (40%) were to women diagnosed before age 18, and 157 (60%) were to women diagnosed as adults. The team manually reviewed electronic medical records to collect information on patient characteristics, disease history, medications, pregnancy

*"Disease activity during pregnancy, rather than age at diagnosis, emerged as a stronger predictor of neonatal outcomes."*

outcomes, and newborn health. The study's two main outcomes were gestational age at delivery and birth-weight percentile.

Overall, neonatal outcomes were favorable. Nearly 9 in 10 infants were born at term, with a median gestational age of 39.1 weeks. The median birth-weight percentile was 50, and just 11% of infants were considered small for gestational age.

The clearest difference between the groups involved fetal growth. Only 4% of infants born to mothers with pediatric-onset Crohn's disease were small for gestational age, compared with 16% of those born to mothers with adult-onset disease. Infants in the pediatric-onset group also had a higher median birth-weight percentile (64 vs. 43). Gestational age at delivery was similar between the groups.

After the researchers accounted for maternal age and other clinical factors, pediatric-onset Crohn's disease was associated with a 16-point increase in birth-weight percentile compared with adult-onset disease. However, age at diagnosis was not associated with differences in gestational age at delivery.

Disease duration also appeared to influence outcomes. For every 10% increase in the proportion of a woman's life spent living with Crohn's disease, the likelihood of delivering a small-for-gestational-age infant decreased by 21%. That association remained largely unchanged after researchers accounted for factors such as biologic therapy, disease type, perianal disease, and mode of delivery.

Disease activity during pregnancy was linked to poorer fetal growth. Women who experienced a Crohn's disease flare requiring corticosteroid treatment or a change in therapy during pregnancy had infants with birth-weight percentiles about 11 points lower than those of women without a flare. Although flares were not associated with gestational age at delivery, the findings support previous research showing that active inflammatory bowel disease (IBD) during pregnancy can adversely affect fetal growth.

Medication use at conception was also associated with neonatal outcomes. Women receiving anti–tumor necrosis factor therapy when they became pregnant had infants with birth-weight percentiles nearly 9 points higher than those of women not receiving biologic therapy. Anti-TNF treatment was also associated with delivery about 0.8 weeks later. The authors noted that women with pediatric-onset Crohn's disease were more likely to be receiving biologic therapy at conception, which may have helped keep disease activity under control during pregnancy.

Pregnancy outcomes were largely similar between the two groups. Rates of disease flare during pregnancy or after delivery, preterm premature rupture of membranes, and intrauterine growth restriction did not differ significantly. However, cesarean delivery was more common among women with pediatric-onset Crohn's disease, occurring in 61% of deliveries compared with 48% among women with adult-onset disease. The researchers suggested that the higher rate of perianal disease among women with pediatric-onset Crohn's disease may help explain the difference.

"I now feel much more confident counseling young women with Crohn's disease about future pregnancy and neonatal outcomes," Dr. Kurowski concluded. "Our findings also provide additional support for the use of early biologic therapy to optimize disease control. Consistent with prior studies, we again confirmed that active disease has a significant negative impact on neonatal outcomes, reinforcing the importance of achieving and maintaining remission before and during pregnancy."

The authors acknowledged several limitations, including the study's retrospective design and incomplete data on disease activity, inflammatory markers, and endoscopic findings. They also noted that miscarriages and spontaneous abortions were likely underreported, as many occurred outside the health system and were therefore not captured in the medical record.

*The study received funding support from The Garber Family Foundation and Athletes vs Crohn's & Colitis. Dr. Kurowski and coauthors reported no relevant conflicts.*

*GI & Hepatology News* invited Sudheer Kumar Vuyyuru, MBBS, MD, DM, an inflammatory bowel disease specialist at Western University, London, Ontario, Canada, to comment on the work.

**What makes this study important?**

**Dr. Vuyyuru:** Approximately one fourth of all Crohn's disease (CD) cases are diagnosed during childhood or adolescence. As many of these individuals reach reproductive age, understanding the impact of pediatric-onset CD on pregnancy outcomes is increasingly important. This study provides timely and meaningful insights for gastroenterologists managing this growing patient population.

**How might the findings influence clinical practice?**

**Dr. Vuyyuru:** The findings are both reassuring and clinically informative. Contrary to expectations, neonates born to mothers with pediatric-onset CD experienced significantly better outcomes than those born to mothers with adult-onset CD, including lower rates of small-for-gestational-age (SGA) infants (3.8% vs. 15.9%, P= 0.02) and higher birth weight percentiles (a mean of 16.2 percentage points). Importantly, disease activity but not age at CD onset emerged as the primary determinant of pregnancy outcomes. These findings offer evidence-based reassurance that women with pediatric-onset CD can expect favorable outcomes when their disease is well controlled, and they underscore the importance of sustained remission as a central component of preconception counseling.

**What questions remain unanswered?**

**Dr. Vuyyuru:** Despite its important contributions, several limitations warrant consideration. The retrospective, single-center design and predominantly Caucasian study population may limit the generalizability of the findings. In addition, disease activity was inconsistently documented in the electronic medical record, resulting in a less rigorous definition of remission. The study also focused exclusively on CD, leaving the impact of pediatric-onset ulcerative colitis on pregnancy outcomes unanswered. Furthermore, with only 105 births among women with pediatric-onset CD, the study was underpowered to detect differences in uncommon outcomes such as preeclampsia and congenital malformations. Future prospective, multicenter studies incorporating validated measures of disease activity, population-based controls, more diverse patient populations, and patient-reported outcomes are needed to confirm these findings and address the remaining evidence gaps.

**Do you have any final thoughts on this work?**

**Dr. Vuyyuru:** The observation that longer disease duration was associated with a lower risk of SGA infants is intriguing and may reflect improved disease control and treatment optimization over time. While hypothesis-generating, these findings merit further evaluation in prospective studies. The study underscores the need for early reproductive counseling in girls diagnosed with pediatric-onset CD, well before they reach childbearing age. Such counseling should address the importance of sustained disease control, the safety of IBD therapies during pregnancy, and the potential fertility implications of prior pelvic surgery.

*Dr. Vuyyuru reported receiving consulting fees from Alimentiv Inc.*

# Upadacitinib linked to clinical and MRI gains in perianal Crohn's disease

First multicenter real-world cohort to report pelvic MRI outcomes finds earlier treatment works better.

By Olivia Anderson

Upadacitinib was associated with clinical response and radiologic improvement in patients with active perianal Crohn's disease, according to a multicenter retrospective study published in *Clinical Gastroenterology and Hepatology*.

The study included 125 patients treated across 10 centers in the United States and Canada and evaluated both clinical outcomes and pelvic magnetic resonance imaging (MRI) findings. According to the authors, real-world data on upadacitinib in perianal Crohn's disease have been limited, and radiologic outcomes had not previously been reported.

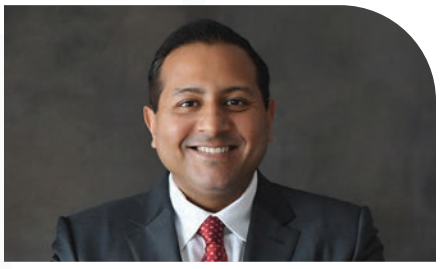
Perianal Crohn's disease affects a substantial proportion of patients with Crohn's disease and can result in fistulas, drainage, abscesses, pain, and fecal incontinence. The authors noted that available treatment options have produced remission in only a minority of patients, highlighting the need for additional therapeutic approaches.

The primary outcome of the study was clinical response, defined as a reduction of at least 3 points in the perianal disease activity index. At the first follow-up visit after upadacitinib induction, 45.5% of patients achieved clinical response and 39.4% achieved clinical remission, according to the study.

Among patients who underwent follow-up pelvic MRI, 55.1% demonstrated radiologic improvement and 11.5% achieved complete healing. Overall, the study found MRI findings improved or healed in approximately two-thirds of patients with available imaging data.

"Treatment with upadacitinib was associated with improved fistula outcomes in patients with perianal Crohn's disease, with greater effectiveness in those anti–tumor necrosis factor-naïve or with shorter disease duration," the authors wrote.

The cohort included a treatment-experienced population. According to the study, nearly half of patients had complex fistulas and most had prior exposure to anti-tumor necrosis factor therapy.



Parakkal Deepak, MD

The authors wrote that "biologic-naïve status and shorter disease duration (≤2 years) were associated with higher clinical response rates," while prior anti-tumor necrosis factor exposure was linked to lower rates of clinical, radiologic, and composite response.

The study also evaluated changes in individual perianal disease activity index domains. According to the authors, improvements were observed in measures of pain, discharge, induration, and activity restriction. The authors noted that symptomatic improvement and anatomic healing may not occur at the same pace.

Study author Parakkal Deepak, MD, said in an interview with *GI & Hepatology News* that the study adds information that was not available from prior analyses of upadacitinib in perianal Crohn's disease.

"This is, to date, the largest real-world, multicenter experience of upadacitinib specifically for perianal Crohn's disease, and the first to report radiologic (pelvic MRI) outcomes," Dr. Deepak said, noting that the current study evaluated both clinical response and MRI-based outcomes in routine clinical practice.

Regarding clinical implications, Dr. Deepak said upadacitinib is a "reasonable, effective option" for perianal fistulizing Crohn's disease in real-world practice and works better the earlier it's used. He also emphasized the role of imaging in treatment assessment.

"Practically, MRI (TOpClass) matters: clinical closure underestimates deep healing, so imaging should inform treat-to-target decisions," he said.

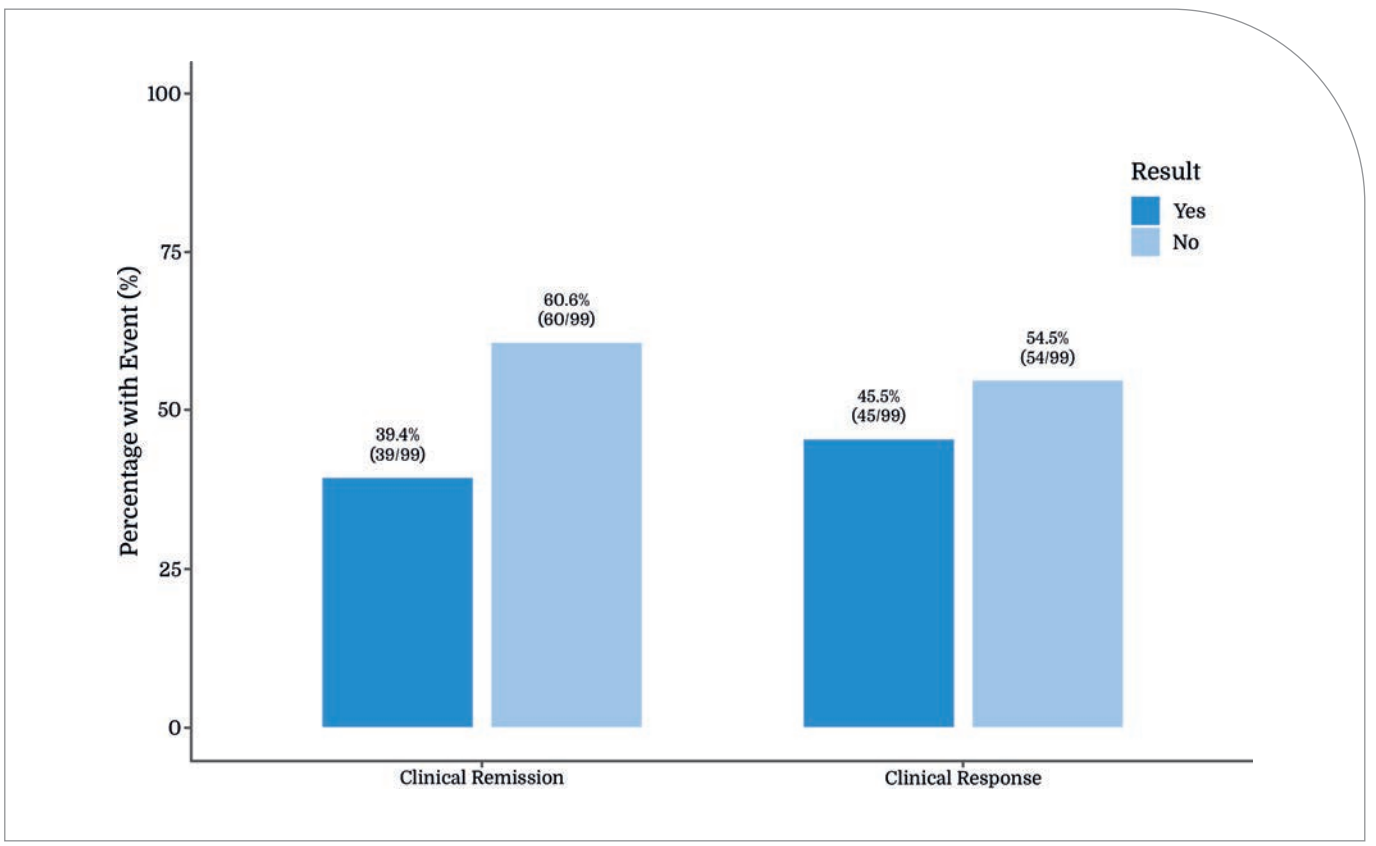
The authors reported low rates of hospitalization, corticosteroid use, and perianal surgery during follow-up. They wrote that these findings "underscore the clinical utility and tolerability of [upadacitinib] in this high-risk population."

The study has several limitations. According to the authors, the retrospective observational design introduces potential bias, follow-up duration was limited, and MRI assessments were available for only a subset of patients. The study also lacked a control group, and concomitant treatments such as antibiotics and seton placement may have influenced outcomes. The authors wrote that the lack of a control group "precludes direct comparisons of effectiveness and limits causal inferences."

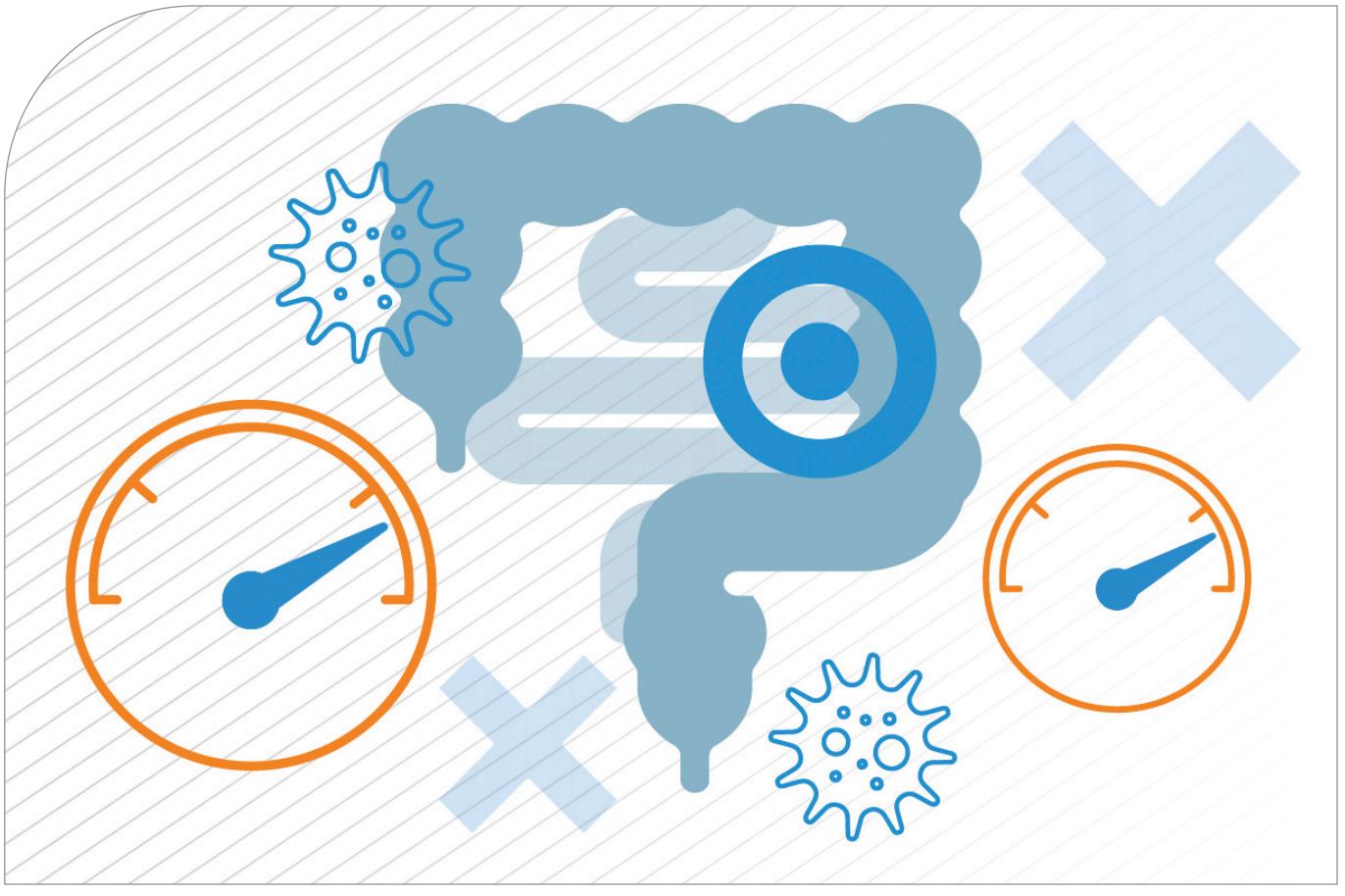
They concluded that upadacitinib was "associated with meaningful clinical and radiologic benefits in patients with pCD, including those with prior biologic exposure," while noting that prospective studies are needed to determine the durability of response over longer follow-up periods and to better define the role of upadacitinib in perianal Crohn's disease.

*Several authors reported financial relationships with companies including AbbVie, Takeda, Pfizer, Bristol Myers Squibb, Janssen, and Eli Lilly. One author also reported royalties from Wolters Kluwer and ties to Covera Health and Roche.*

*"Upadacitinib is a reasonable, effective option for perianal fistulizing Crohn's disease in real-world practice and works better the earlier it's used."*




Percentage of patients achieving clinical remission or response at first follow-up. Figure courtesy of *Clinical Gastroenterology and Hepatology*.



# Bowel-wall thickness predicted steroid failure in pediatric severe colitis

Children with left-colon wall thickness above 5 mm were far more likely to fail steroids and proceed to surgery.

By Doug Brunk

A bedside intestinal ultrasound scan (IUS) performed within the first 48 hours of treatment predicted which children with acute severe ulcerative colitis would not respond to corticosteroids more accurately than standard clinical assessment tools, a prospective study found.

The findings, published in *Gastroenterology*, suggest that a rapid, noninvasive bedside examination could help physicians make earlier treatment decisions in a condition where delays may increase the risk of complications and surgery.

Paolo Lionetti, MD, PhD, of the gastroenterology and nutrition unit at Meyer Children's Hospital, Florence, Italy, and colleagues enrolled 60 children with acute severe ulcerative colitis who had not previously received biologic therapy. The patients were treated at 10 pediatric inflammatory bowel disease centers across Europe between 2020 and 2024. All had a Pediatric Ulcerative Colitis Activity Index (PUCAI) score of 65 or higher and received intravenous corticosteroids as the initial treatment, in line with current clinical guidelines.

Each patient underwent two IUS examinations: one within 48 hours of starting corticosteroid treatment and a second between days 5 and 7. Researchers assessed several signs of intestinal inflammation, including colon wall thickness, blood flow in the bowel wall, preservation of bowel wall layers, inflammation of nearby tissue, enlarged lymph nodes, and the Milan Ultrasound Score, which combines wall thickness and blood flow measurements. Treating physicians were not informed of the ultrasound results during the study.

Nearly two-thirds of children in the study (39 of 60) did not respond to corticosteroid treatment and needed additional therapy with infliximab. Ten eventually required surgery to remove their colon within eight weeks because their disease could not be controlled with medication.

The clearest early predictor of corticosteroid failure on IUS was identified in the left side of the colon. At the first ultrasound exam, children who did not respond to corticosteroids had significantly thicker bowel wall measurements in the left lower quadrant than those who responded, with median measurements of 6 mm compared with 4.2 mm ($P < .001$). Similar differences were seen in the left upper quadrant. Nonresponders also showed increased blood flow in the bowel wall more often on Doppler ultrasound, a sign of active inflammation.

A bowel wall thickness greater than 5 mm in the lower left quadrant was the best cutoff for predicting corticosteroid failure. Using this threshold, ultrasound correctly identified 85% of patients who did not subsequently respond to steroids and correctly ruled out steroid failure in 67% of those who did respond. The Milan Ultrasound Score performed similarly. A score above 7.8 predicted steroid resistance with 83% sensitivity and 71% specificity.

Notably, both ultrasound measures predicted corticosteroid failure more accurately than the PUCAI score measured at the same time. They also outperformed commonly used blood tests for inflammation, including erythrocyte sedimentation rate and C-reactive protein.

The second ultrasound examination provided another way to identify patients at high risk for poor outcomes. Children who eventually required colectomy continued to show signs of active inflammation on ultrasound, including greater wall thickness, increased vascularity, loss of bowel wall stratification, mesenteritis, and enlarged lymph nodes.

By days five to seven, a left lower quadrant wall thickness greater than 4.8 mm predicted failure of medical treatment with 100% sensitivity. Similarly, a Milan Ultrasound Score above 8.7 identified all patients who ultimately required colectomy or further escalation of treatment. Both ultrasound measures again performed better than the PUCAI score.

The ultrasound findings were also linked to longer-term outcomes. Among patients who did not require colectomy, those who achieved steroid-free clinical remission by eight weeks had significantly reduced left lower quadrant wall thickness and lower Milan Ultrasound Scores on the second ultrasound examination. Lower scores were also associated with the combined outcome of steroid-free remission and fecal calprotectin normalization.

The authors noted several limitations, including the relatively small number of patients, the use of different ultrasound operators and equipment across study sites, and the lack of follow-up beyond eight weeks. Comparisons with endoscopy were also limited because full colonoscopy is generally avoided during episodes of acute severe disease.

Even so, the findings suggest that bedside IUS could play a valuable role during a critical period of treatment, when decisions about escalating therapy can have major consequences for patient outcomes.

"IUS may provide valuable, noninvasive information for early identification of corticosteroid resistance and poor short-term outcomes in pediatric ASUC," the authors concluded. They also noted that incorporation of colonic wall thickness and Milan Ultrasound Score into routine care pathways "may optimize risk stratification, guide timely escalation of therapy, and support clinical decision-making in this vulnerable population."

*No external funding was received for this study. Several authors reported relationships with pharmaceutical and nutrition companies, including advisory board service, research grants, consulting fees, honoraria, royalties, and speaker fees.*

# Substance use disorders in gastroenterology and hepatology: A practical guide for the general gastroenterologist

Isabelle S. Byers, MD; Michelle Russin, MD; Sasha Deutsch-Link, MD, MSCR

## Introduction

Substance use disorders (SUDs) represent one of the most prevalent chronic diseases in the United States and are a major driver of morbidity and mortality across a spectrum of gastrointestinal (GI) and liver diseases. SUD is defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as a cluster of cognitive, behavioral, and physiological symptoms in which an individual continues using a substance despite significant substance-related problems.[1] In 2024, approximately 48 million people in the United States met criteria for an SUD, yet most did not receive specialty treatment.[2]

As patients with SUDs may initially present with GI-related complaints, GI providers are uniquely positioned to intervene during these encounters. The purpose of this review is to equip the general gastroenterologist and hepatologist with the knowledge and tools needed to identify SUDs, initiate evidence-based treatment, and connect patients to longitudinal care.

## GI and liver manifestations of SUDs

### Alcohol

Alcohol consumption is associated with a range of GI and liver-related diseases. Alcohol-associated liver disease (ALD) encompasses a broad spectrum of disease from isolated steatosis to cirrhosis.[3] ALD is now the leading indication for liver transplantation in the United States, and its morbidity and mortality continue to rise.[4] Beyond the liver, alcohol reduces lower esophageal sphincter pressure, contributing to gastroesophageal reflux and erosive esophagitis. Ethanol and its metabolites also directly injure pancreatic acinar and ductal cells, causing premature enzyme activation and inflammation that underlie both acute and chronic pancreatitis. Alcohol use further confers an elevated risk of esophageal, gastric, and colorectal cancers.[5]

### Opioids

Opioids are implicated in a range of GI disorders through their effects on the enteric nervous system that disrupt motility, secretory and sphincteric function, and intestinal barrier integrity.[6] In the esophagus, opioids can induce distal esophageal spasm, type III achalasia, or esophagogastric junction outflow obstruction by impairing inhibitory neurons in the myenteric plexus. In the stomach and duodenum, opioids delay gastric emptying and impair motility, which can cause nausea and vomiting, early satiety, and postprandial fullness, known as opioid-induced gastroparesis.[7] Opioids also reduce colonic peristalsis and intestinal secretions, prolong transit, and lead to dyssynergic defecation, which can result in opioid-induced constipation (OIC).[6] Narcotic bowel syndrome is an underrecognized disorder of gut-brain interaction in which abdominal pain progresses and paradoxically worsens with continued opioid use.[8] Conversely, opioid withdrawal drives noradrenergic rebound in the enteric nervous system, leading to nausea, vomiting, abdominal cramping, and diarrhea.[9] These symptoms can mimic other acute GI processes, so opioid withdrawal should remain on the differential when they are present.

Intravenous drug use associated with opioid use disorder (OUD) drives the majority of new hepatitis C virus (HCV) infections in the United States. Untreated HCV causes hepatic fibrosis in a significant proportion of individuals, with roughly 20% to 30% developing cirrhosis over 20 to 30 years.[10]

### Cannabis

Cannabis use is increasingly common among patients with GI symptoms, and many patients specifically self-medicate with cannabis to treat nausea, vomiting, or abdominal pain. Cannabinoids act via CB1 and CB2 receptors throughout the enteric nervous system, modulating motility, secretion, visceral pain, and inflammation. With chronic, daily use, patients can develop cannabis hyperemesis syndrome (CHS), characterized by cyclical episodes of severe nausea, vomiting and abdominal pain.[11] Because patients often use cannabis specifically for these same symptoms, they may be reluctant to consider it as the cause, and may even increase use in response to worsening symptoms, making cessation counseling challenging in practice.

### Tobacco

Tobacco use disorder independently worsens GI and hepatic outcomes. With effects mediated by oxidative stress, immune dysregulation and oncogenic pathways driven by numerous carcinogens, tobacco use is a risk factor for esophageal, gastric, pancreatic, and colorectal cancers.[12] Tobacco use is also associated with an increased risk of peptic ulcer disease, Crohn's disease, acute and chronic pancreatitis, and pancreatic exocrine insufficiency. Smoking also promotes hepatic fibrosis, increases the risk of hepatocellular carcinoma and worsens post-transplant outcomes.[13]

## Management of SUD in GI practice

### Recognizing and diagnosing SUD

The first step in managing GI and liver-related complications of SUDs involves SUD screening and diagnosis. Validated screening tools for SUDs can be easily integrated into GI clinic workflows. For alcohol, the Single Alcohol Screening Questionnaire (SASQ) or AUDIT-C (a three-item condensed version of the Alcohol Use Disorders Identification Test) demonstrate high sensitivity and can be administered in less than one minute.[14] For opioids, the Drug Abuse Screening Test (DAST-10) or single-question screens such as "How often in the past year have you used drugs other than as prescribed?" provide rapid risk stratification.[15] Formal SUD diagnosis under DSM-5 criteria requires identifying at least two of 11 criteria within a 12-month period.[1]

### SBIRT: A framework for intervention

Screening, Brief Intervention and Referral to Treatment (SBIRT) is an evidence-based, public health approach to identify, engage, and refer patients to treatment. The three-step model involves: (1) Screening using a validated tool; (2) a Brief Intervention — a focused, nonjudgmental conversation lasting five to 15 minutes that provides feedback, raises awareness of health consequences, and explores motivation for change; and (3) Referral to Treatment for patients with moderate-to-severe SUD.[16]

As part of brief intervention in GI clinics, motivational interviewing (MI) should be incorporated to build rapport with patients and enhance motivation for behavior change. MI can be described using the "OARS" acronym: Open-ended questions; Affirmations of positive thoughts, actions, or ideas; Reflections that indicate you hear and understand; and Summarizing basic reflections.[16] See Table 1 for a review of these principles in a case example adapted from Deutsch-Link et al.[17]

For referral to treatment, the Substance Abuse and Mental Health Services Administration's findtreatment.gov is a publicly available, searchable database of local treatment facilities that clinicians can share directly with patients. Another option is performing warm handoffs to primary care providers for ongoing coordination of care.

### Medications for alcohol use disorder

Despite robust evidence for efficacy, medications for alcohol use disorder (AUD), or MAUD, remain underutilized. There are three FDA-approved medications for AUD: naltrexone, acamprosate, and disulfiram. However, disulfiram should be avoided in liver disease due to the risk of hepatotoxicity.

Naltrexone, available as a once-daily oral tablet or monthly intramuscular injection (Vivitrol), is a first-line agent. Though historically avoided in liver disease, multiple retrospective studies now support its safety in ALD, including in decompensated disease (Child-Pugh Class B/C).[18] Of note, naltrexone is contraindicated in patients on chronic opioids or opioid agonist therapy (methadone or buprenorphine).

Acamprosate is another first-line MAUD and, due to primary renal excretion, represents an excellent option for patients with decompensated cirrhosis and preserved renal function. For patients with severe renal impairment (CrCl ≤30 mL/min), acamprosate is contraindicated. Baclofen, a GABA-B agonist with predominantly renal clearance, is the only MAUD with randomized trial data in cirrhosis, although studies have demonstrated mixed efficacy. Gabapentin and topiramate, both used off-label, offer additional options for patients who cannot tolerate first-line agents or who have co-occurring pain or sleep disturbances.[17]

A recent meta-analysis of randomized controlled trials in patients with AUD and cirrhosis

| Motivational interviewing principle | Example statements | Clinical intent |
|---|---|---|
| Open-ended questions | "Can you tell me what role alcohol plays in your life right now?" / "What concerns, if any, do you have about your drinking since being diagnosed with cirrhosis?" | Elicit patient perspective; invite discussion without judgment |
| Affirmations of positive thoughts, actions or ideas | "You've been dealing with a lot medically, and it's clear you've been doing your best to manage everything." / "It sounds like you've made changes before when things have felt urgent." | Reinforce strengths; build rapport and trust |
| Reflections that indicate you hear and understand | "It sounds like alcohol helps you cope with stress, even though you worry about the impact on your liver." / "I'm hearing you feel pressured to stop alcohol, but you're not sure you're ready." | Demonstrate understanding and reduce defensiveness |
| Summarizing basic reflections | "Let me make sure I'm understanding: Alcohol helps you relax and feel normal, but you're also worried about worsening your liver disease and your overall health." | Consolidate ambivalence and transition to change talk |
| Express empathy | "Given all that you are dealing with and the stress of your diagnosis, it makes sense that trying to stop using alcohol feels overwhelming." | Normalize ambivalence and maintain therapeutic alliance |
| Rolling with resistance | "I hear that stopping alcohol completely feels really hard right now. Would it be okay if we explore what feels hardest about stopping?" | Acknowledge resistance and shift from resistance to exploration (with permission) |
| Elicit change talk | "How does your drinking fit with what you want your health to look like in a year?" / "On a scale of 1 to 10, how important is it to you to protect your liver? I'm hearing a 7 — and why not a lower number?" | Encourage patient-generated motivation |
| Link behavior to liver disease | "Would it be okay if I shared how alcohol affects cirrhosis, and then hear your thoughts?" | Provide education with permission |
| Collaborative planning | "What would feel like a reasonable next step for you?" / "Would you be open to talking with someone who specializes in alcohol use while we continue managing your liver disease?" | Maintain patient autonomy and integrate addiction care |

Table 1. Motivational interviewing for gastroenterologists and hepatologists.
*Case example: A patient with compensated alcohol-associated cirrhosis continues to consume alcohol and expresses ambivalence/resistance after counseling about liver-related risks.*

showed that MAUD use was associated with a 32% increase in alcohol abstinence.[19] We encourage GI clinicians to incorporate MAUD into the care of patients with ALD. GI clinics represent an underutilized opportunity to expand access to safe and effective treatment.

**Medications for opioid use disorder**
Medications for opioid use disorder (MOUD) — buprenorphine, methadone, and extended-release naltrexone — are the most effective treatments for OUD and reduce overdose mortality by more than 50%. Historically, buprenorphine required a special DEA waiver (the "X-waiver"), but this was eliminated in 2023, meaning any prescriber with a standard DEA registration can now prescribe buprenorphine for OUD.[2]

GI providers who feel comfortable may prescribe buprenorphine as a bridge prescription — a short-term course (typically one to four weeks) to stabilize a patient in withdrawal and link them to a primary prescriber or addiction medicine program. Otherwise, the essential role is to screen for OUD, engage the patient without stigma, and provide a warm handoff to addiction medicine, primary care, or a bridge clinic. The findtreatment.gov website identifies OUD treatment programs by ZIP code. Of note, buprenorphine is generally considered safe in patients with compensated liver disease and can be used with appropriate monitoring in more advanced disease.

For OIC, stimulant or osmotic laxatives should be initiated early. When ineffective, peripherally acting μ-opioid receptor antagonists (PAMORAs), including oral naloxegol (Movantik) or methylnaltrexone (Relistor, available as subcutaneous or oral formulations), are evidence-based treatment options that can substantially improve symptoms.[6]

**Cannabis hyperemesis syndrome**
The only definitive treatment for CHS is cannabis cessation — a fact that must be communicated clearly and compassionately to patients — though several adjunctive agents can improve symptoms while patients work on abstinence. In the acute setting, haloperidol, droperidol, and topical capsaicin (applied to the abdomen) have demonstrated symptom relief. Benzodiazepines and aprepitant have also shown benefit in case series and small studies. Standard antiemetics and opioids have not demonstrated significant benefit. Finally, amitriptyline, which is used in idiopathic cyclic vomiting syndrome, may be considered in patients who experience difficulty stopping cannabis.[11]

**Tobacco cessation strategies**
Tobacco cessation counseling is among the highest-yield interventions available to GI clinicians and offers meaningful risk reduction. The "5 A's" framework — Ask, Advise, Assess, Assist, and Arrange — is one practical approach. Even brief physician counseling (fewer than three minutes) meaningfully increases quit rates, and the combination of behavioral counseling with pharmacotherapy is substantially more effective than either modality alone.[20]

Varenicline (Chantix), a partial agonist at the α4β2 nicotinic acetylcholine receptor, is the most effective single agent for tobacco cessation. Nicotine replacement therapy remains a first-line option and is particularly well-suited for patients with prior intolerance to varenicline.[21] Providers should also offer a referral to the National Cancer Institute's quitline (1-800-QUIT-NOW) or the text-based SmokefreeTXT program, both of which provide structured support at no cost to the patient.

## Conclusions

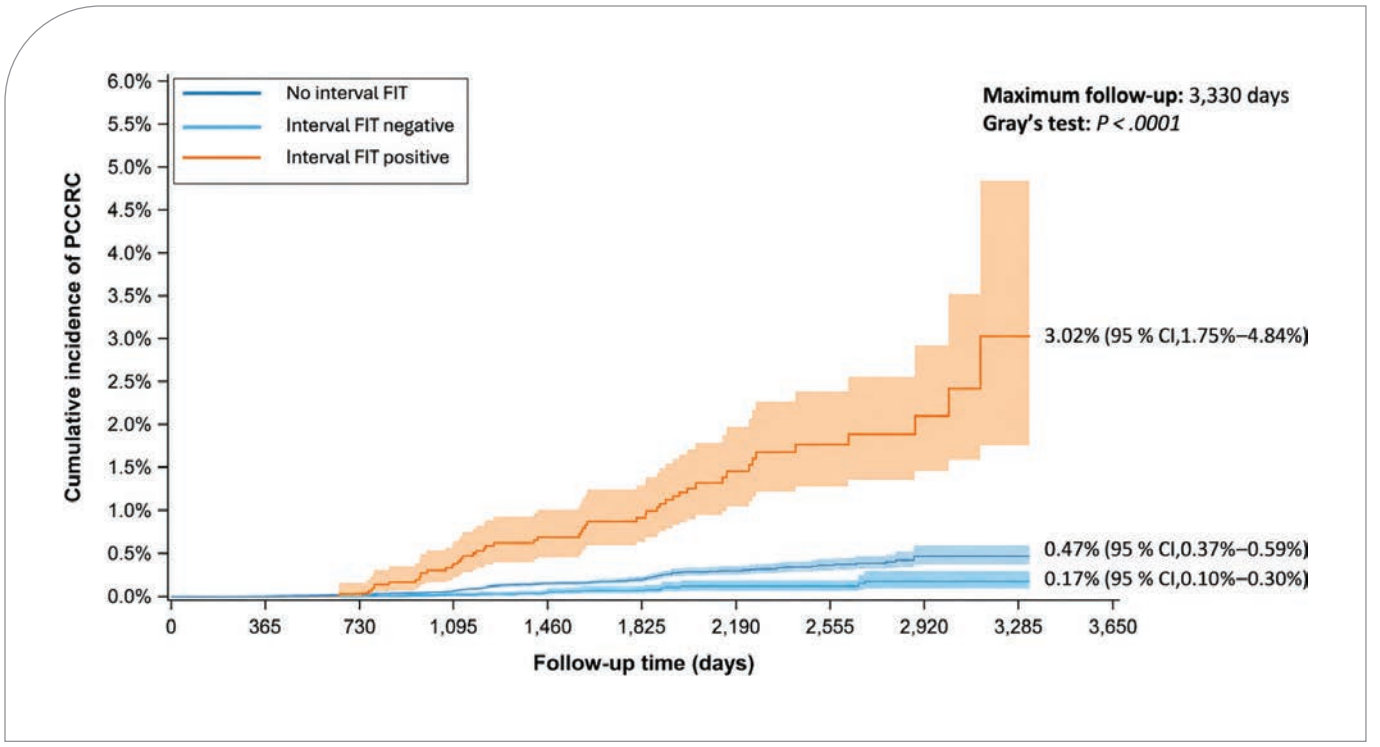
Ultimately, gastroenterologists and hepatologists routinely encounter patients at sentinel moments along the care trajectory — a new diagnosis of alcohol-associated hepatitis, a hospitalization for opioid-induced bowel dysfunction, an episode of cannabis hyperemesis, or a complication of acute pancreatitis. These moments can serve as powerful catalysts for SUD treatment engagement. The gastroenterologist or hepatologist who recognizes this opportunity, and is equipped with the screening tools and prescribing knowledge to act on it, can fundamentally alter the course of a patient's disease. Closing the gap between SUD identification and treatment initiation requires a workforce of GI clinicians who are trained to screen for SUD, initiate a brief intervention, and connect patients to evidence-based treatment.

*References are available in the online article.*

# Study supports repeat colonoscopy after positive interval FIT following colonoscopy

Patients with a positive interval FIT had a higher rate of post-colonoscopy colorectal cancer than those who tested negative or weren't tested, according to a British Columbia cohort study.

By Olivia Anderson




Cumulative total CRC incidence estimated by the cumulative incidence function, adjusting for competing risk of death, by interval FIT group. Figure courtesy of *Clinical Gastroenterology and Hepatology.*

Jennifer J. Telford, MD, MPH, FRCPC, CAGF, FACG

Patients who had a positive fecal immunochemical test (FIT) after a colonoscopy and before they were due for their next recommended screening or surveillance examination had a higher risk of post-colonoscopy colorectal cancer (PCCRC) than patients who had no interval FIT or a negative interval FIT, according to a population-based study published in *Clinical Gastroenterology and Hepatology*.

During a median follow-up of approximately 43 months, 275 of 169,117 patients developed PCCRC. The cumulative incidence of PCCRC was 0.47% among patients who did not undergo interval FIT testing, 0.17% among those with a negative interval FIT, and 3.02% among those with a positive interval FIT, according to the study.

"This study demonstrates that patients who have a positive fecal immunochemical test (FIT) after a colonoscopy and before they are next due for colon screening are at higher risk of colorectal cancer when compared to patients who have an interval negative FIT or do not have FIT performed," lead author Jennifer J. Telford, MD, MPH, FRCPC, CAGF, FACG, told *GI & Hepatology News*. "The key takeaway is that despite a recent colonoscopy, patients with a positive FIT should be offered repeat colonoscopy."

The authors wrote that the optimal management of patients with an unplanned positive FIT after colonoscopy remains uncertain. Although U.S. and European guidelines suggest considering repeat colonoscopy in this setting, those recommendations have been based on limited evidence.

To evaluate the association between interval FIT results and PCCRC risk, investigators conducted a retrospective cohort study using data from the British Columbia Colon Screening Program. The analysis included 169,117 patients who underwent colonoscopy between 2013 and 2021. Patients with incomplete colonoscopy, inflammatory bowel disease, or a personal history of colorectal cancer were excluded.

The primary outcome was PCCRC, defined as colorectal cancer diagnosed more than six months after the index colonoscopy and before the end of the recommended screening or surveillance interval. Among study participants, about 15% completed a FIT after colonoscopy but before they were due for repeat screening or surveillance. Most of those tests were negative, while a smaller proportion were positive.

After adjustment for demographic characteristics, family history, prior colonoscopy history, colonoscopy findings , and other factors, patients with a positive interval FIT remained at significantly increased risk of PCCRC compared with patients who did not undergo interval FIT testing. By contrast, a negative interval FIT was associated with a lower risk.

*"The key takeaway is that despite a recent colonoscopy, patients with a positive FIT should be offered repeat colonoscopy."*

"Patients with a positive interval FIT are at increased risk of PCCRC and should be offered repeat colonoscopy," the authors concluded.

The association remained consistent across multiple sensitivity analyses. Investigators also accounted for differences in follow-up time and variation among physicians performing colonoscopy.

According to the authors, patients with a positive interval FIT who underwent an additional colonoscopy before a PCCRC diagnosis continued to have an elevated risk compared with patients who did not undergo interval FIT testing, although the risk was lower than that observed in the overall interval FIT-positive group. "The risk of PCCRC was reduced, but still significant, for patients in the interval FIT positive group who had an additional colonoscopy between their index colonoscopy and PCCRC diagnosis," the authors wrote.

The study was conducted within an organized screening program that does not recommend routine interval FIT testing for patients already enrolled in colonoscopy surveillance or for those not yet due for repeat screening. However, interval FIT testing still occurred in a subset of patients, allowing investigators to evaluate outcomes associated with positive and negative test results.

The authors identified several strengths of the study, including its large sample size, population-based design, detailed colonoscopy data, and linkage with a provincial cancer registry. They wrote that these features improved the accuracy of risk estimates and minimized the risk of missing cancer diagnoses.

The authors acknowledged that the study's retrospective design limited the ability to account for all factors associated with colorectal cancer risk. In addition, the indication for interval FIT testing was unknown. According to the authors, some FITs may have been ordered because patients lacked a regular primary care provider, while others may have been used to investigate symptoms. The authors also noted that the findings should be interpreted in the context of local screening practices, including FIT positivity thresholds and underlying colorectal cancer prevalence.

*The authors reported having no disclosures.*

# Oakland score showed highest specificity for safe discharge in lower GI bleeding

In a prospective multicenter Canadian study, a score of 8 or less identified patients who could be discharged from the ED, though it was less sensitive than clinical judgment.

By Doug Brunk

A prospective multicenter Canadian study found that the Oakland score was the most specific risk stratification tool for identifying patients with lower gastrointestinal bleeding who could be safely discharged from the emergency department, outperforming clinical judgment and other competing risk scores. The findings support using the score alongside physician assessment when making discharge decisions.

"This study matters because it provides physicians with a tool to help safely discharge patients from the emergency department," first author Michael Sey, MD, MPH, FRCP(C), of the division of gastroenterology at Western University, London, Ontario, Canada, told *GI & Hepatology News*. "Although most patients with lower gastrointestinal bleeding do well, a small percentage can rebleed and develop serious adverse events. This tool, along with sound clinical judgement, helps the attending physician risk stratify and identify patients who can be safely managed as outpatients with appropriate follow-up."

Michael Sey, MD, MPH, FRCP(C)

For the study, published in *Clinical Gastroenterology and Hepatology*, Dr. Sey and colleagues included 344 adults who came to eight Canadian hospitals with signs of lower gastrointestinal bleeding, including bright red blood from the rectum or maroon-colored stool, between September 2019 and February 2024. The researchers followed patients for 28 days after presentation.

The average age of participants was 59 years. Women made up 48% of the group, and 42% were admitted to the hospital when they first sought care. Nearly 20% were taking antiplatelet medications, and 12% were using anticoagulants.

During the 28-day follow-up period, 16 patients were readmitted to the hospital, 41 required blood transfusions, and 24 underwent endoscopic procedures to stop bleeding. Two patients needed radiologic intervention, and 12 required surgery. Five patients died within 28 days of presentation; however, investigators reported that none of the deaths were directly caused by lower GI bleeding.

The researchers compared the Oakland score with other tools used to assess bleeding risk, including the Strate, BLEED, Glasgow-Blatchford, and clinical Rockall scores. They also compared these tools with physicians' judgments about whether patients could be safely discharged. The NOBLADS score was not included in the analysis because serum albumin levels were not available for most patients.

Using area under the receiver operating characteristic curve (AUROC) analysis, the Glasgow-Blatchford score demonstrated the highest overall discrimination at 0.81, followed by the Oakland score at 0.77 and clinical judgment at 0.76. The Strate score achieved an AUROC of 0.68, the clinical Rockall score 0.63, and the BLEED score 0.62. The Oakland score performed similarly to physicians' clinical judgment, with no statistically significant difference between the two. However, the Oakland score was significantly more accurate than the BLEED and clinical Rockall scores.

Because clinicians rely on specific score cutoffs when making decisions, the researchers also assessed performance at validated thresholds. An Oakland score of 8 or less had the highest specificity (95%), followed by the Glasgow-Blatchford score (88%) and clinical judgment (81%). Clinical judgment had the highest sensitivity (70%), followed by the Glasgow-Blatchford score (50%) and BLEED score (48%). The Oakland score's lower sensitivity (23%) reflects its focus on safe discharge.

"We were surprised by how well the Glasgow-Blatchford Bleeding score performed," Dr. Sey said. "Although it was developed almost three decades ago for upper gastrointestinal bleeding, it was still quite discriminative for the prediction of safe discharge in lower GI bleeding."

The researchers noted that specificity may be more important than sensitivity in this setting because incorrectly classifying high-risk patients as safe for discharge could lead to adverse outcomes. Clinical judgment incorrectly identified 16 unsafe patients as suitable for discharge, compared with four patients classified as safe by the Oakland score.

Dr. Sey added that the study's findings "will provide reassurance to physicians, both GI and non-GI alike, that lower gastrointestinal bleeding patients who score 8 or less on the Oakland score can be safely discharged for outpatient care provided there are appropriate discharge instructions and follow-up plans."

Several additional analyses supported the main findings. The results remained unchanged after accounting for missing data and after excluding digital rectal examination findings from the Oakland score. Researchers also found no meaningful differences in outcomes between patients enrolled during versus after the COVID-19 pandemic or between those enrolled on weekdays vs. weekends.

Among patients who underwent colonoscopy, hemorrhoidal bleeding was the most common diagnosis, accounting for 22% of cases, followed by diverticular bleeding at 20%.

The researchers noted several limitations, including missing digital rectal examination data, possible underreporting of minor rebleeding events treated outside the hospital, differences in transfusion practices, and variation in physicians' discharge decisions.

*The study was funded by an Innovation Grant from the Academic Health Sciences Centre in Ontario, Canada. Coauthor Harminder Singh, MD, MPH, reported advisory or consulting relationships with Pendopharm, Amgen Canada, AbbVie Canada, Innomar, Sandoz Canada, Takeda Canada, and Guardant Health unrelated to the study. All other authors reported no relevant conflicts of interest.*

Credit: Unsplash.com

# Celiac care nears a turning point in screening and treatment, expert says

Many patients continue to experience symptoms and life disruptions despite a gluten-free diet, fueling demand for better options.

By Doug Brunk

Advances in celiac disease research and care could soon reshape how patients are diagnosed, monitored, and treated, Dan Leffler, MD, MS, AGAF, said during the keynote address at a virtual policy symposium hosted by the Society for the Study of Celiac Disease and the Celiac Disease Foundation.

"We are really in an exciting transitional period in celiac disease," said Dr. Leffler, executive medical director and global program lead for celiac disease at Chugai Pharmaceuticals and associate professor of medicine at Harvard Medical School. "A lot of pieces are coming together. The celiac population is growing and is poised to grow even further. Limitations of the gluten-free diet are increasingly clear. Therapies and new diagnoses are coming."

Opening the session, Dawn Adams,

Dan Leffler, MD, MS, AGAF

MD, MS, CNSC, a gastroenterologist at Vanderbilt University Medical Center and president of the Society for the Study of Celiac Disease, emphasized the need for alternatives to the gluten-free diet. She described celiac disease as a condition in which "for some, the burden of treatment is actually greater than the benefits of treating the disease." She said ongoing discussions among experts are essential to ensure that future therapies can benefit a broad range of patients rather than only narrowly defined subgroups.

Dr. Leffler noted that celiac disease affects roughly 1% of the global population and carries substantial clinical, psychosocial, and economic consequences. In addition to facing an increased risk of death and several serious comorbidities, patients must manage the daily challenges of adhering to a strict gluten-free diet.

As celiac disease prevalence continues to rise, Dr. Leffler pointed to the emergence of population-based screening efforts in the United States and Europe as an encouraging development. "Celiac disease screening programs, after years and years of discussion, are really beginning in the US and Europe," he said. "I believe this has the potential to result in the biggest increase in celiac disease diagnosis since tTG [tissue transglutaminase] testing became widely available."

Population-based screening efforts could greatly increase the number of patients diagnosed with celiac disease and referred to gastroenterology practices, Dr. Leffler said. But diagnosing the condition remains a challenge. Many adults wait six to 10 years for a diagnosis, he said, and are often given other diagnoses first, such as irritable bowel syndrome, food sensitivities, eating disorders, or stress-related conditions. Even today, he noted, fewer than half of people with celiac disease in the United States have been diagnosed.

Dr. Leffler also challenged the belief that most patients do well on a gluten-free diet alone. Citing a recent survey of 2,001 Americans with biopsy-confirmed celiac disease who had followed a gluten-free diet for at least 12 months, he said that 85% reported experiencing gluten-related symptoms at least once during the previous three months.

"What was really impressive, and even to me somewhat shocking, was the amount of functional impairment that these gluten exposures caused," Dr. Leffler said. "About 75% of them experienced life impacts, such as missing work, school, reduced work function, for at least a couple days."

Those findings underscore the substantial societal burden of accidental gluten exposure, Dr. Leffler said.

"If you imagine that most people are getting exposed to gluten every month or every couple months from this survey, and most of those are having at least a few days of reduced ability to work or go to school, this actually becomes a significant impact on the patients, on their families, on society in general," he said.

Patients are increasingly interested in treatment options beyond simply avoiding gluten, Dr. Leffler said. Surveys he cited show that about 90% of patients would like a therapy that could either replace or be used alongside a gluten-free diet. Most patients aren't looking to eat gluten freely, he said, but rather want protection against accidental gluten exposure.

Researchers have also gained a better understanding of the wide range of experiences among people with celiac disease.

"We used to just think about celiac disease as one disease, and you put everyone on a diet," Dr. Leffler said. "We now recognize it's really a spectrum of patients and their response to celiac disease and response to gluten-free diet."

One advantage for drug developers, he continued, is that celiac disease is one of the most thoroughly understood immune-related disorders. Researchers have a clear picture of how the disease develops, from the way gluten is processed in the body to the immune reactions that damage the intestine. This deeper understanding has fueled the development of a wide range of potential therapies.

Although larazotide acetate and other promising agents have failed to reach approval, Dr. Leffler said the field has learned valuable lessons about trial design.

"Celiac disease is not inflammatory bowel disease, and trial design cannot be assumed to be similar," he said. Investigators have also learned that symptoms do not necessarily reflect active celiac disease, that patients alter their behavior when enrolled in clinical trials, and that histologic damage correlates poorly with symptom severity.

Beyond therapeutics, Dr. Leffler pointed to advances in gluten immunogenic peptide testing, proteomic and transcriptomic assessment of intestinal injury, cytokine-based diagnostic approaches, and population-management tools derived from real-world and electronic medical record data.

Still, he cautioned that realizing the promise of these innovations will require coordination among clinicians, researchers, regulators, payers, patient advocates, and patients themselves.

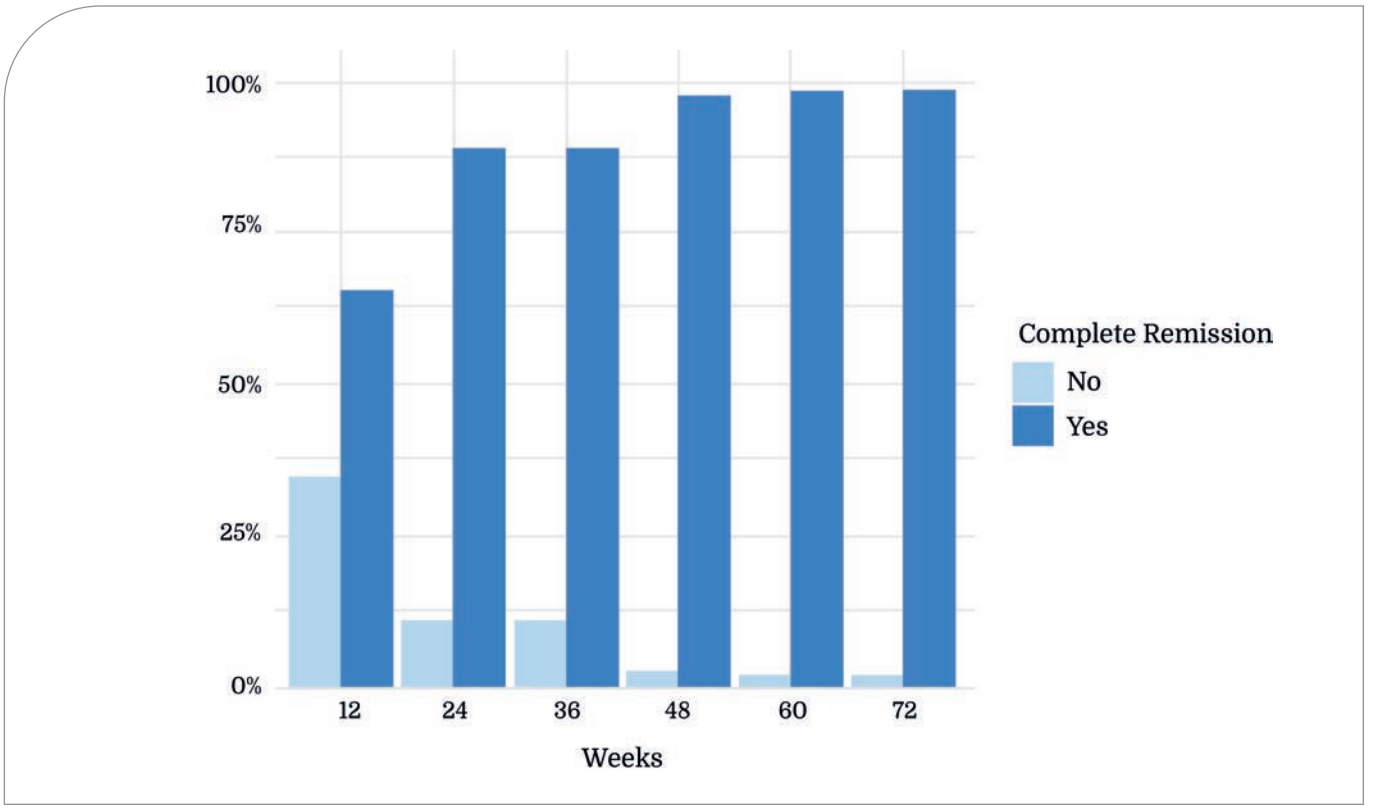
"We need different stakeholders coming together early and often if we're going to realize the potential new developments and really build a better future for everyone with celiac disease," Dr. Leffler said.

*Dr. Leffler is a board member of the Foundation for Celiac Disease Outcome Measures.*

# Long-term dupilumab associated with sustained remission in refractory eosinophilic esophagitis

Real-world 72-week study shows sustained clinical, endoscopic, and histologic improvement in disease activity.

By Olivia Anderson




Percentage of patients with and without complete remission over time. Figure courtesy of *Clinical Gastroenterology and Hepatology.*

Long-term treatment with dupilumab was associated with sustained clinical, endoscopic, and histologic remission in pediatric and adult patients with eosinophilic esophagitis (EoE), according to results from the retrospective multicenter DUPEOETALY study published in *Clinical Gastroenterology and Hepatology*.

The observational study evaluated 167 patients with confirmed EoE treated at 50 Italian pediatric and adult gastroenterology, allergy, and clinical immunology centers between 2023 and 2024. According to the study, patients received dupilumab through compassionate-use or off-label programs before regulatory approval for EoE in Italy.

The median age at dupilumab initiation was 21.5 years, and 77.8% of patients were male. Investigators reported that 76% of patients had a personal history of atopy. Before treatment with dupilumab, 94% of patients had received proton pump inhibitors, and 86.2% had received topical corticosteroids. According to the study, nonresponse rates to proton pump inhibitors and topical corticosteroids were 96.8% and 92.4%, respectively.

Kristle Lynch, MD, of the University of Pennsylvania and a member of the AGA Quality Committee, told *GI & Hepatology News* that the findings add meaningful real-world context to the existing trial data.

"The DUPEOETALY study provides real-world evidence that long-term dupilumab therapy can achieve sustained and near-complete remission in patients with EoE," Dr. Lynch said. She noted the cohort included patients who were refractory or intolerant to prior treatments such as proton pump inhibitors and topical corticosteroids.

Investigators assessed symptoms using the dysphagia symptom questionnaire, endoscopic severity using the EoE endoscopic reference score, and histologic activity using peak eosinophil counts per high-power field (eos/HPF). Outcomes were evaluated at baseline and at weeks 12, 24, 36, 48, 60, and 72.

According to the study, all primary outcomes improved significantly over time. The least squares mean dysphagia symptom questionnaire score decreased from 22.14 at baseline to 4.94 at week 12 and 0.21 at week 72 ($P < .001$). Peak eosinophil counts decreased from a mean of 36.80 eos/HPF at baseline to 2.03 eos/HPF at week 12, reaching −0.64 eos/HPF at week 72 ($P < .001$). The mean EoE endoscopic reference score decreased from 3.95 at baseline to −0.07 at week 12 ($P < .001$), which investigators wrote reflected "near-complete endoscopic resolution of inflammation and remodeling features across the population."

The authors defined complete remission as a dysphagia symptom questionnaire score of five or less, endoscopic reference score of two or less, and fewer than 15 eos/HPF. According to the study, 73% of patients achieved composite remission at week 12, with remission rates exceeding 90% from week 24 onward. By week 72, 98.3% of patients met the study's remission criteria.

The investigators reported that treatment response did not significantly differ according to sex, diagnostic delay, prior esophageal dilation, or personal history of atopy. Baseline eosinophil count also was not significantly associated with treatment response. However, higher baseline dysphagia symptom questionnaire and endoscopic reference scores were associated with lower odds of achieving complete remission at week 12, according to multivariable analysis.

*"The DUPEOETALY study provides real-world evidence that long-term dupilumab therapy can achieve sustained and near-complete remission in patients with EoE."*

The authors reported that patients with fibrostenotic features, including esophageal rings, strictures, or prior dilation, were included in the cohort. In the discussion, they noted clinical and endoscopic improvements in patients with fibrostenotic disease during dupilumab treatment.

Safety findings were favorable throughout follow-up. According to the study, six patients (3.8%) experienced adverse events, including three cases of injection-site reactions, two episodes of transient arthralgia, and one case of mild conjunctivitis. No serious adverse events were reported, and no patients discontinued treatment because of intolerance.

Dr. Lynch said the findings may affect long-term management strategies for refractory disease. "For clinicians, the key takeaway is that dupilumab offers a highly effective steroid-sparing targeted therapy capable of improving multiple aspects of EoE simultaneously, in patients refractory to prior therapy," she said. "These findings may influence patient care by encouraging long-term maintenance treatment strategies and advancing a more personalized approach to EoE management focused on sustained disease remission."

The authors acknowledged several limitations, including the retrospective study design, the lack of standardized follow-up schedules, and the absence of centralized histologic review. The authors also noted that dupilumab frequently was initiated alongside ongoing therapies, including proton pump inhibitors, topical corticosteroids, or dietary interventions, which may affect interpretation of treatment outcomes.

*Dupilumab was provided free through Sanofi's Managed Access Program. Sanofi had no role in study design, data collection, analysis, or reporting but had the opportunity to review the manuscript before submission. Several authors reported speaker, consultant, or advisory relationships with Sanofi/Regeneron and other pharmaceutical companies.*

# FDA approves olezarsen to reduce acute pancreatitis risk in severe hypertriglyceridemia

Tryngolza becomes the first therapy shown to lower the rate of acute pancreatitis in adults with triglycerides of at least 500 mg/dL, broadening an indication first granted for familial chylomicronemia syndrome in 2024.

By Bob Alaburda

The US Food and Drug Administration has approved olezarsen (Tryngolza) as an adjunct to diet to reduce triglycerides and the risk of acute pancreatitis in adults with severe hypertriglyceridemia (sHTG), making it the first agent shown to lower acute pancreatitis risk in this population.

The decision, which came ahead of the drug's June 30 target action date, expands the label for olezarsen, an antisense oligonucleotide the agency first cleared in December 2024 for adults with familial chylomicronemia syndrome (FCS), a rare genetic form of sHTG. The new indication covers the much larger sHTG population, defined by fasting triglyceride levels of at least 500 mg/dL, well above the normal threshold of less than 150 mg/dL.

For gastroenterologists, the clinical relevance is the pancreatitis signal. Hypertriglyceridemia is a recognized cause of acute pancreatitis, and CORE/CORE2 showed that olezarsen significantly reduced acute pancreatitis events in adults with severe hypertriglyceridemia — a clinical endpoint not previously demonstrated in sHTG phase 3 trials of triglyceride-lowering therapy.

## Mechanism

Olezarsen is a ligand-conjugated antisense oligonucleotide that reduces hepatic production of apolipoprotein C-III (apoC-III), a protein that regulates triglyceride metabolism. Lowering apoC-III increases clearance of triglyceride-rich lipoproteins. It is administered as a once-monthly subcutaneous injection.

## Trial data

The approval rests on two phase 3, randomized, double-blind, placebo-controlled trials — CORE (CORE-TIMI 72a) and CORE2 (CORE2-TIMI 72b) — that together enrolled 1,061 adults with sHTG and a mean baseline triglyceride level of 1,116 mg/dL. The primary endpoint in both trials was the percent change in fasting triglycerides from baseline to month 6 versus placebo.

In CORE, placebo-adjusted reductions in triglycerides were 63% for the 50-mg dose and 72% for the 80-mg dose. In CORE2, the corresponding reductions were 49% and 55%. In a pooled analysis of the two trials, the incidence of acute pancreatitis was significantly lower with olezarsen than with placebo (rate ratio, 0.15; 95% CI, 0.05–0.40; P < .001), according to the results published in the *New England Journal of Medicine*.

## Safety

The most common adverse reactions were injection-site reactions and liver enzyme elevations. The FDA advises liver enzyme testing before starting therapy or increasing the dose, and as clinically indicated thereafter; persistent elevations may warrant dose interruption or reduction.

Allergic reactions — including skin redness, hives, facial swelling, chills, or trouble breathing — have been reported. Clinicians should counsel patients on the signs and symptoms of these reactions and instruct them to seek medical attention promptly and discontinue olezarsen if they occur.

# Repeat fibrosis screening more than halves missed cases in type 2 diabetes

A prospective cohort validating the AGA Clinical Care Pathway found the false-negative rate dropped from 7% to 3% with two-year reassessment.

By Alun Evans

Repeating noninvasive fibrosis assessments every two years may substantially reduce missed cases of significant liver fibrosis among adults with type 2 diabetes, according to a prospective longitudinal study in *Gastro Hep Advances* validating the AGA Clinical Care Pathway for metabolic dysfunction-associated steatotic liver disease (MASLD).

Individuals with type 2 diabetes are at increased risk for MASLD and progressive liver fibrosis, making effective screening strategies a clinical priority. Current AGA and American Association for the Study of Liver Diseases guidance recommends a stepwise approach using the fibrosis-4 index (FIB-4), followed by vibration-controlled transient elastography (VCTE)

Veeral Ajmera, MD

in patients with indeterminate results, with reassessment every two to three years for those considered low risk.

"The AGA Clinical Care Pathway has been widely endorsed for non-invasive fibrosis risk stratification, and our cross-sectional work previously showed it performed well in patients with T2DM," said Veeral Ajmera, MD, study co-author and an investigator at University of California San Diego's MASLD Research Center. "However, the guidelines recommend reassessing low-risk patients every two to three years, and there were limited data supporting that. Given that patients with T2DM are at especially high risk for fibrosis progression, we wanted to evaluate how serial reassessment affects two key metrics: the false negative rate and the number of patients referred to specialty care."

To achieve this aim, Dr. Ajmera and his colleagues at the MASLD Research Center evaluated 209 adults aged 50 to 79 years with type 2 diabetes who underwent baseline and two-year follow-up assessments. Magnetic resonance elastography (MRE), an imaging-based measure of liver stiffness, served as the reference standard for significant fibrosis, defined as liver stiffness of at least 3.3 kPa. In this instance, Dr. Ajmera noted, MRE was used as a research reference standard rather than as a recommended screening tool.

At the study's baseline, nearly 70% of participants had MASLD and 19% had significant fibrosis. Applying the AGA pathway classified 52.8% of patients as low risk, 42.1% as indeterminate risk, and 5.0% as high risk. The pathway produced a false-negative rate of 7%, meaning that nine patients classified as low risk were found to have significant fibrosis on MRE. Only 17.6% of participants met criteria for referral to specialty care.

After repeat testing two years later, the false-negative rate declined to 3%. Among the patients initially categorized as low risk, 88.3% remained low risk, while others were appropriately reclassified into higher-risk categories. Additionally, most patients who were falsely classified as low risk at baseline were correctly reclassified during follow-up. Of the nine baseline false-negative cases, only two remained false negatives after repeat evaluation.

"This is a strong, real-world endorsement of the guideline-recommended two-to-three-year reassessment interval," said Dr. Ajmera, "which meaningfully reduces misclassification without overwhelming hepatology clinics."

The investigators also examined whether lowering the FIB-4 threshold from 1.3 to 1.0 could improve detection. Dr. Ajmera stressed that clinicians should pay close attention to patients falling within this threshold, particularly those who have elevated ALT (alanine aminotransferase) or AST (aspartate aminotransferase). "Nearly all of our missed cases at baseline fell in this range," he added. "A lower FIB-4 cutoff of 1.0 essentially eliminated false negatives, but at the cost of a 54% increase in downstream VCTE testing. Therefore, individualized judgment, particularly when transaminases are elevated, is still recommended."

"Serial reassessment works and the AGA Clinical Care Pathway is not meant to be applied once," Dr. Ajmera said. "Its accuracy improves when repeated at the recommended interval, and patients initially classified as low-risk should be re-evaluated rather than considered permanently cleared."

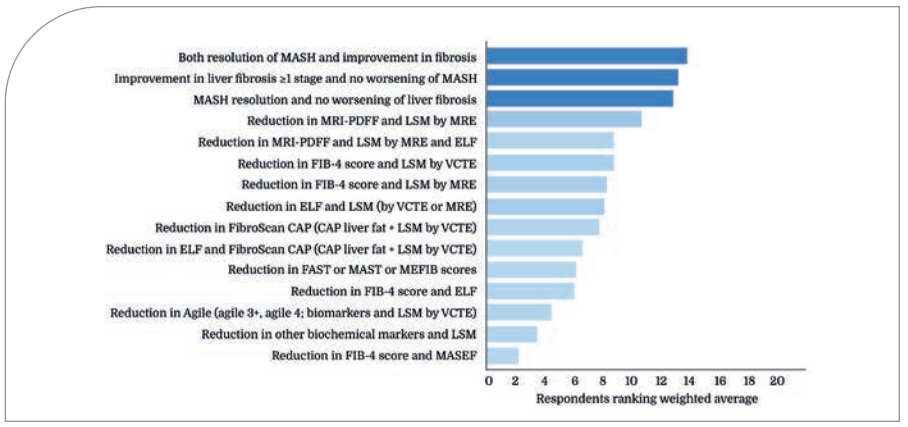
He added that optimal reassessment intervals and FIB-4 thresholds still remain "open questions," and that future research needs to also look at the cost-effectiveness of a direct-to-VCTE approach for high-risk patients, including those with lower FIB-4 cutoffs and type 2 diabetes.

*Dr. Ajmera reported consulting for Madrigal Pharmaceuticals and having been awarded research grants from Gilead Sciences. Study co-author Rohit Loomba reported consulting and research relationships with multiple pharmaceutical companies. The remaining authors reported no relevant conflicts of interest.*

# Delphi panel backs liver stiffness measures for monitoring MASH therapy

Experts said noninvasive tests may help clinicians track treatment response in routine practice, but prospective validation is still needed.

By Doug Brunk




Surrogate endpoints and potential surrogate outcome measures ranked in order of importance for assessing both disease activity and/or liver fibrosis in MASH. Figure courtesy of *Clinical Gastroenterology and Hepatology.*

An international panel of metabolic dysfunction-associated steatohepatitis (MASH) experts reached consensus that noninvasive tests, particularly liver stiffness measurement, may be useful for assessing treatment response in routine clinical practice and could reduce reliance on serial liver biopsies.

The findings, published in *Clinical Gastroenterology and Hepatology*, come from a modified Delphi consensus study involving 23 experts from 10 countries who evaluated surrogate endpoints for assessing treatment efficacy in MASH across regulatory, reimbursement, and clinical practice settings.

"Given the growing MASH therapeutic landscape, with ongoing phase III trials including semaglutide, survodutide, lanifibranor, pegozafermin, efruxifermin, and resmetirom, among others, defining appropriate surrogate endpoints is increasingly critical," wrote first author Arun J. Sanyal, MD, of Virginia Commonwealth University, Richmond, and colleagues.

Current regulatory guidelines focus on liver biopsy results, specifically either a one-stage improvement in fibrosis without worsening MASH or resolution of MASH without worsening fibrosis. In the first Delphi survey round, 77% of experts agreed that these biopsy-based measures are still important indicators of treatment effectiveness. At the same time, experts expressed strong support for shifting toward noninvasive tests (NITs) that assess hepatic fibrosis rather than inflammation. Eighty-five percent agreed that NITs are the best way to assess how well treatment is working, and 80% agreed that NITs should replace liver biopsy as the preferred method for measuring treatment outcomes in patients with MASH.

Consensus was defined as agreement among at least 75% of panelists, while strong consensus required agreement from at least 95%.

Among the available NITs, liver stiffness measurement (LSM) using vibration-controlled transient elastography (VCTE) or magnetic resonance elastography (MRE) was identified as the leading candidate endpoint. In the second survey round, which focused on clinical practice, 95% of experts agreed that reductions in LSM are an important way to assess treatment effectiveness and may serve as a surrogate marker for long-term outcomes. All panelists agreed that current evidence links lower LSM values with better long-term patient outcomes.

Experts also endorsed specific response thresholds. Specifically, 94% agreed that a 30% decrease or increase in LSM is associated with a corresponding reduction or increase in risk for adverse clinical outcomes. In addition, 82% agreed that a 0.5-point change in the enhanced liver fibrosis (ELF) score has similar value in predicting future clinical outcomes.

When experts evaluated potential surrogate endpoints, they showed greater support for measures that assess hepatic fibrosis than for markers that reflect disease activity alone. Consensus was reached for both traditional histologic endpoints and a combined imaging endpoint that included reductions in magnetic resonance imaging–proton density fat fraction (MRI-PDFF) and LSM by MRE, with 77% agreement for each.

"In routine clinical practice, NITs were considered important for assessing treatment effectiveness and as potential surrogate outcomes," the researchers wrote. "Their expanding role underscores the need for clear guidance to facilitate wider implementation."

The authors noted several limitations, including the lack of direct discussion among panelists inherent to the Delphi process and the reliance on expert opinion rather than head-to-head comparisons of surrogate endpoints. They also emphasized the need for prospective studies to confirm that changes in noninvasive markers predict long-term clinical outcomes before these measures can gain broader regulatory acceptance.

*The study was funded by Novo Nordisk. Two coauthors were employed by Novo Nordisk, and multiple authors reported consulting fees, advisory roles, research funding, speaker fees, stock ownership, or other relationships with pharmaceutical and biotechnology companies involved in MASH drug development.*

*GI & Hepatology News* invited Robert Fontana, MD, professor of medicine and director of the transplant hepatology fellowship program at University of Michigan Health, to weigh in on the study.

**Why is this study important?**

**Dr. Fontana:** We need to have quantitative, simple, reliable, and widely available tools in clinical practice to know where we are going in managing individual MASH patients. As the study authors point out, although liver biopsy is the gold standard for clinical trials, this does not translate well to clinical practice for several reasons. Firstly, liver biopsy is limited by sampling artifact. It is also invasive, costly, and most patients do not like to undergo serial biopsies. With so many MASH patients, it is also not practical to biopsy everyone.

There are multiple proposed NITs to use for treatment efficacy, and they all have advantages and disadvantages, but there is no single NIT to use. This is reflected in the variability of Delphi expert opinion results. MR-based methods (MRI-PDFF and MRE) are probably the most accurate and reliable. However, they are not widely available outside of major medical centers and are extremely costly and cumbersome. So although perhaps the most accurate, MRI is not currently practical or scalable. LSM using VCTE is more widely available, simple to obtain as a POC test, and affordable. However, it is not as accurate as MRI and there are more causes of false-positive results (alcohol use) and patient factors (high BMI) that are limitations. Lastly, the panel and other experts agree that serum ELF testing and FIB-4 are not well established enough to hang your hat on by themselves.

In clinical practice, most of us use an imaging-based biomarker (MRI or VCTE) in combination with blood biomarkers (transaminases, serum ELF panel) and do not use liver biopsies at all to assess treatment response. So, this paper will likely be cited by practitioners, insurers, and other groups regarding "consensus recommendations" on how to monitor treatment and disease progression going forward.

**How might the findings influence clinical practice?**

**Dr. Fontana:** The paper provides a relative ranking of various options as seen by an expert panel. Again, insurers, hospitals, and physicians will likely find this useful information to guide their clinical practice, establish practice patterns, and inform equipment purchasing and development of NITs.

*Dr. Fontana is a member of the AASLD MASLD Special Interest Group. He also conducts research funded by Fractyl and Takeda, and he consults for Roche, Intellius, MasterSwitch, and eGenesis.*

# Jeffry Nestler, MD, on the true calling of clinical care

**2026 AGA Distinguished Clinician Award honoree Jeffry Nestler, MD, reflects on private practice, advanced endoscopy, colorectal cancer prevention and building systems that put patients first.**

For more than 35 years, Jeffry Nestler, MD, has worked at the intersection of private practice, advanced endoscopy and health system leadership. As president of Connecticut GI and co-physician-in-chief of the Hartford HealthCare Digestive Health Institute, he has helped build coordinated models of care while continuing to care for patients with complex pancreatobiliary disease.

Beyond his practice and health system roles, Dr. Nestler serves as associate clinical professor at the University of Connecticut School of Medicine and has been a visible advocate for independent GI practice and for colorectal cancer screening. This year, he received AGA's Distinguished Clinician Award in Private Practice, an honor recognizing physicians who demonstrate exemplary leadership and dedication to patient care outside an academic setting.

In a conversation with *GI & Hepatology News*, Dr. Nestler reflected on what the award means to him, why he remains committed to hands-on clinical practice and what he hopes the next generation of gastroenterologists will carry forward.

*"The greatest satisfaction in medicine doesn't come from titles or recognition; it comes from knowing that a patient leaves healthier, with hope, and better than when they came to you."*

**Congratulations on AGA's Distinguished Clinician Award in Private Practice. When the news reached you, what did you most hope the award was recognizing about your work?**

**Dr. Nestler:** When I learned that I had been selected for the AGA Distinguished Clinician Award in Private Practice, I hoped it recognized the breadth of my career's work in advancing the quality of care for my patients while fostering a culture of collaboration among my colleagues. Throughout my career, I have believed that the best patient outcomes are achieved through teamwork, shared purpose, adoption of innovation and a commitment to continuous improvement. This recognition reflects not only my individual efforts but also the collective accomplishments of the outstanding physicians and health care professionals with whom I have had the privilege to work.

**For readers who know you by your titles but not your path, what first drew you to gastroenterology, and what's kept you in it across 35 years?**

**Dr. Nestler:** Gastroenterology drew me because it provided the opportunity to care for patients of all ages with a wide range of illnesses, allowing me to build long-term relationships while making a meaningful difference in their lives. It is also a specialty that has continually been at the forefront of innovation, combining advances in technology with creativity in diagnosis and treatment. More than 35 years later, what has kept me engaged is the constant evolution of the field and the opportunity to continually improve the care we provide to our patients. As excited as I was about the specialty in the beginning, I am more excited about the future of our profession.

**You've spent decades as a practice president, a hospital GI chief and an institute co-leader, and you're still doing advanced endoscopy and complex pancreatobiliary work yourself. What keeps you at the table for the hardest cases, and what does staying hands-on give you that the leadership roles can't?**

**Dr. Nestler:** I have always loved taking care of patients — that is why I went to medical school. Even after decades in leadership roles, caring for patients remains the most fulfilling part of what I do. Continuing to perform advanced endoscopy and manage complex pancreatobiliary cases keeps me connected to the challenges and rewards of clinical practice. Being a practicing physician gives me a perspective that complements my leadership roles. It allows me to make decisions based on firsthand experience, understand the realities facing physicians and patients, and ensure that my leadership remains grounded in what matters most — delivering the highest-quality patient care. It provides a unique perspective that I believe physician leaders should have.

**Without identifying details, is there a case or patient interaction that changed how you practice or what you believe good GI care should feel like from the patient's side?**

**Dr. Nestler:** There have been several patients throughout my career whose lives were saved because they received timely, advanced endoscopic intervention when other options were limited. Those experiences reinforced for me the importance of continually advancing our field and ensuring that patients have access to the latest technologies and expertise. Seeing those patients recover, leave the hospital with their families, and return to their lives has been among the most rewarding moments of my career. Seeing a patient be able to walk with their grandchild on the beach again makes it all worth it. It has also shaped my belief that exceptional GI care is not just about technical excellence — it is about delivering the right care at the right time with compassion, urgency and hope.

**The Digestive Health Institute was built around coordinated, multidisciplinary care. What problem with the old way were you trying to fix, and what does that model change for a patient walking in the door?**

**Dr. Nestler:** The goal was to create a truly coordinated model of care that makes it easier for patients to receive the right care at the right time. As medicine has become increasingly complex, no single physician can provide every aspect of a patient's care. Years ago, a phone call between colleagues was often enough to coordinate treatment. Today, with increasing specialization and the demands on physicians' time, that approach is no longer sufficient.

A multidisciplinary model brings gastroenterologists, surgeons, oncologists, radiologists, pathologists, and other specialists together to develop a unified care plan. Equally important are patient navigators, who help coordinate appointments, testing, and communication so patients and their families don't have to navigate a complicated health care system on their own. The result is a smoother experience, more timely care, better communication among providers, and, ultimately, better outcomes for our patients.

**You've been a public voice on colorectal cancer screening, from the move to age 45 to the noise around colonoscopy evidence. How do you cut through the confusion for patients when guidelines, test options, and headlines seem to conflict?**

**Dr. Nestler:** Colorectal cancer remains one of the leading causes of cancer-related death, but it is also one of the most preventable cancers. My message to patients is straightforward: The best screening test is the one that gets done, because any screening is better than no screening at all. However, it's important to understand the only preventive test is colonoscopy.

Colonoscopy is unique because it is both a screening and preventive test. It not only detects cancer but also allows us to identify and remove precancerous polyps before they ever become cancer. While stool-based tests play an important role and can detect existing cancer or advanced precancerous lesions, they cannot prevent cancer in the same way. My philosophy has always been simple: I would much rather prevent colorectal cancer than diagnose it after it has already developed.

**You've spent much of your career building and defending independent GI practice. What does private practice still do better than anyone, and where does it genuinely need partners — hospitals, academics, management platforms, advocacy — to serve patients well?**

**Dr. Nestler:** I have always believed that the greatest strength of private practice is that it keeps clinical decision-making in the hands of physicians, allowing us to do what is best for our patients without unnecessary barriers. That said, I don't really think of it as "independent" practice — I think of it as interdependent practice. No physician or practice can provide comprehensive care in a vacuum.

Providing the highest-quality care requires strong partnerships with hospitals, health systems, academic centers, and other health care organizations. Complex patients benefit when diverse specialists and subspecialists work together in a coordinated, collaborative way. Private practice brings agility, innovation, and close patient relationships, while our partners provide complementary expertise and resources. When those relationships are built on mutual respect and a shared commitment to excellence, everyone benefits — but most importantly, our patients receive the best possible care. In the end, it should always be about putting patients first.

**As you look at today's fellows and the next decade of GI, what do you most hope they carry forward, and what's the next thing you still want to help build?**

**Dr. Nestler:** My hope is that today's fellows never lose sight of why they went to medical school. Medicine is a profession and a calling — not just a job. While technology, innovation, and the business of health care will continue to evolve, our primary responsibility must always be to our patients.

I hope the next generation carries forward a commitment to compassion, excellence and putting patients first. The greatest satisfaction in medicine doesn't come from titles or recognition — it comes from knowing that a patient leaves your office or the hospital healthier, with hope, and better than when they came to you. If we can instill that mindset in the next generation of gastroenterologists, the future of our specialty will be in very good hands.

As for me, I still want to help build systems of care that make it easier for physicians to provide exceptional, coordinated, patient-centered care while mentoring the next generation of leaders who will continue to advance our specialty. I want to remove the barriers that exist to care so physicians can decide what is right for their patients.

**About the AGA Distinguished Clinician Award**

*Established in 1996, AGA's Distinguished Clinician Awards recognize two members of the practicing community — one in private practice and one in an academic setting — who combine the art of medicine with the skills demanded by the scientific body of knowledge in service to their patients. Nominees must devote the majority of their professional effort to direct patient care and hold current AGA membership.*

*Recipients are selected by the AGA Recognition Prizes Panel, drawn from several of the association's institute committees, and ratified by the AGA Governing Board. The honor recognizes physicians who exemplify leadership and excellence in gastroenterology and who demonstrate outstanding medical proficiency through patient advocacy, innovation in care, the building of clinical programs, and the mentorship of other clinicians.*

*Dr. Nestler received the 2026 private-practice award alongside William M. Lee, MD, honored in the academic category, with both recognized at the AGA Awards Ceremony during Digestive Disease Week® (DDW).*

## Lightning round

**What is the best piece of advice you have given or received?**

Never give up on your dreams.

**What advice do you wish you could give to your younger self?**

Life is a marathon, not a sprint.

Keep moving ahead and pushing the envelope.

**What is your favorite inspiring quote or words to live by?**

"Success is not measured by what you accomplish but by the lives you touch."

**What is your ideal way to spend a day off away from the office?**

On my boat with family and friends.

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