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Ozanimod for Moderate-Severe Ulcerative Colitis: Rethinking the Top-Down Treatment Algorithm

IBD

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This summary reviews Sandborn WJ, Feagan BG, D'Haens G, et al. Ozanimod for Induction and Maintenance of Ulcerative Colitis. *N Engl J Med* 2021; 385: 1280-91.

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STRUCTURED ABSTRACT

Question: Is ozanimod (Zeposia; Bristol Myers Squibb, Princeton, NJ), a selective sphingosine-1-phosphate receptor modulator, superior to placebo for induction and maintenance of remission in moderately to severely active ulcerative colitis (UC)?

Design: To assess induction of remission at 10 weeks, a multi-center, double-blind, placebo-controlled randomized controlled trial (RCT) was conducted, followed by a 42-week, multi-center, double-blind, placebo controlled RCT for UC patients with clinical response to assess maintenance of remission (True North study). Additionally, an additional cohort of moderate-severe UC patients received open-label ozanimod for 10 weeks in order to ensure an adequate sample size for the maintenance of remission RCT.

Setting: RCTs completed in 285 sites in 30 countries between May 2015 and June 2020.

Patients: In the induction of remission RCT, patients were: (a) 18-75 years old; (b) confirmed UC diagnosis ≥ 90 days; (c) moderate-severe UC based on a total Mayo Score of 6-12 with endoscopic subscore of 2-3, rectal bleeding subscore ≥ 1 , and stool frequency subscore ≥ 1 [†]. Exclusion criteria included active or chronic infection, clinically significant cardiovascular condition, history of uveitis or macular edema, and prior history of failing to induce remission with ≥ 2 biologic agents. For the maintenance of remission RCT, patients had to at least achieve clinical response, defined as reduction in total Mayo Score of ≥ 3 points and $\geq 30\%$ from baseline or similar modification using 3-component Mayo Score. All study patients had to have positive IgG antibody for varicella-zoster virus or complete varicella-zoster vaccination.

Interventions/Exposure: In the induction of remission RCT, patients were randomized 2:1 to ozanimod 0.92 mg po qd vs placebo for 10 weeks. In the maintenance of remission RCT, UC patients who achieved clinical response were randomized 1:1 to ozanimod 0.92 mg or placebo through week 52. A 7-day dose escalation was used with ozanimod initiation to minimize risk of bradycardia: 0.23 mg on days 1-4, 0.46 mg on days 5-7 and 0.92 mg thereafter.

Outcome: The primary endpoint was clinical remission using a 3-component Mayo Score and defined as: rectal-bleeding subscore = 0; stool-frequency subscore ≤ 1 with a decrease of at least 1 from baseline; and, an endoscopy subscore ≤ 1 . Key secondary endpoints assessed during induction of remission RCT were: (a) clinical response; (b) endoscopic improvement, defined as endoscopy subscore ≤ 1 without friability; and, (c) mucosal healing, defined as endoscopic improvement plus histologic remission.^{††} In addition to standard safety analyses, pre-specified adverse events of interest were serious or opportunistic infection, cancer, bradycardia, heart block, macular edema, pulmonary and hepatic effects with pulmonary-function testing, ophthalmologic examination, electrocardiogram (ECG), leukocyte counts, and liver function tests (LFTs) performed before and during the trial.

Data Analysis: Modified intention-to-treat analysis defined as patients who were randomized and received at least 1 dose of study medication was performed for the primary endpoints with a 2-sided Cochran-Mantel-Haenszel test. The key secondary endpoints were assessed in a closed,

prespecified hierarchical procedure.^{‡‡} Safety analysis was performed for any patient who received study medication in both induction and maintenance RCTs.

Funding: Bristol Myers Squibb Pharmaceuticals, manufacturers of ozanimod.

Results: Six hundred forty-five patients were enrolled and included in efficacy analysis for the induction of remission RCT. Patient characteristics included male: 60%, mean age: 41-42, mean disease duration: 6.8 years, mean total Mayo Score at baseline = 8.9, and prior anti-TNF therapy = 30%. Clinical remission was significantly more common with ozanimod 0.92 mg po qd vs placebo for induction of remission (18.4% vs 6.0%, $P < 0.001$) and for all key secondary endpoints (**Figure 1**). For the maintenance of remission RCT, which included additional UC patients who achieved clinical response in an open-label cohort, 457 patients were randomized, and ozanimod was again superior to placebo for maintenance of remission: 37.0% vs 18.5%, $P < 0.001$.

Frequency of serious infections were similar in the ozanimod and placebo groups in the induction and maintenance RCTs and was $< 2\%$ in all groups. Absolute lymphocyte count decreased by a mean of 54% in the ozanimod-treated patients during induction of remission RCT. Elevated liver aminotransferase levels were more common with ozanimod vs placebo. Macular edema was reported in 3 patients, but this resolved after discontinuing therapy. No episodes of heart block were recorded. Although patients had to have varicella-zoster vaccination or IgG antibody, herpes zoster infection occurred in 2.2% of ozanimod-treated patients in the maintenance of remission RCT.

NOTES

[‡]The Mayo Score assesses rectal bleeding score (0-3), stool frequency score (0-3), endoscopy sub score (0-3), and Physician's Global Assessment (0-3), with a score range 0-12, with 12 representing most severe UC.

^{‡‡}Although these trials used a classic double-blind, placebo-controlled, randomized study design with modified ITT analysis, study methodology and results are too detailed to summarize comprehensively. Readers are encouraged to review the full study publication.

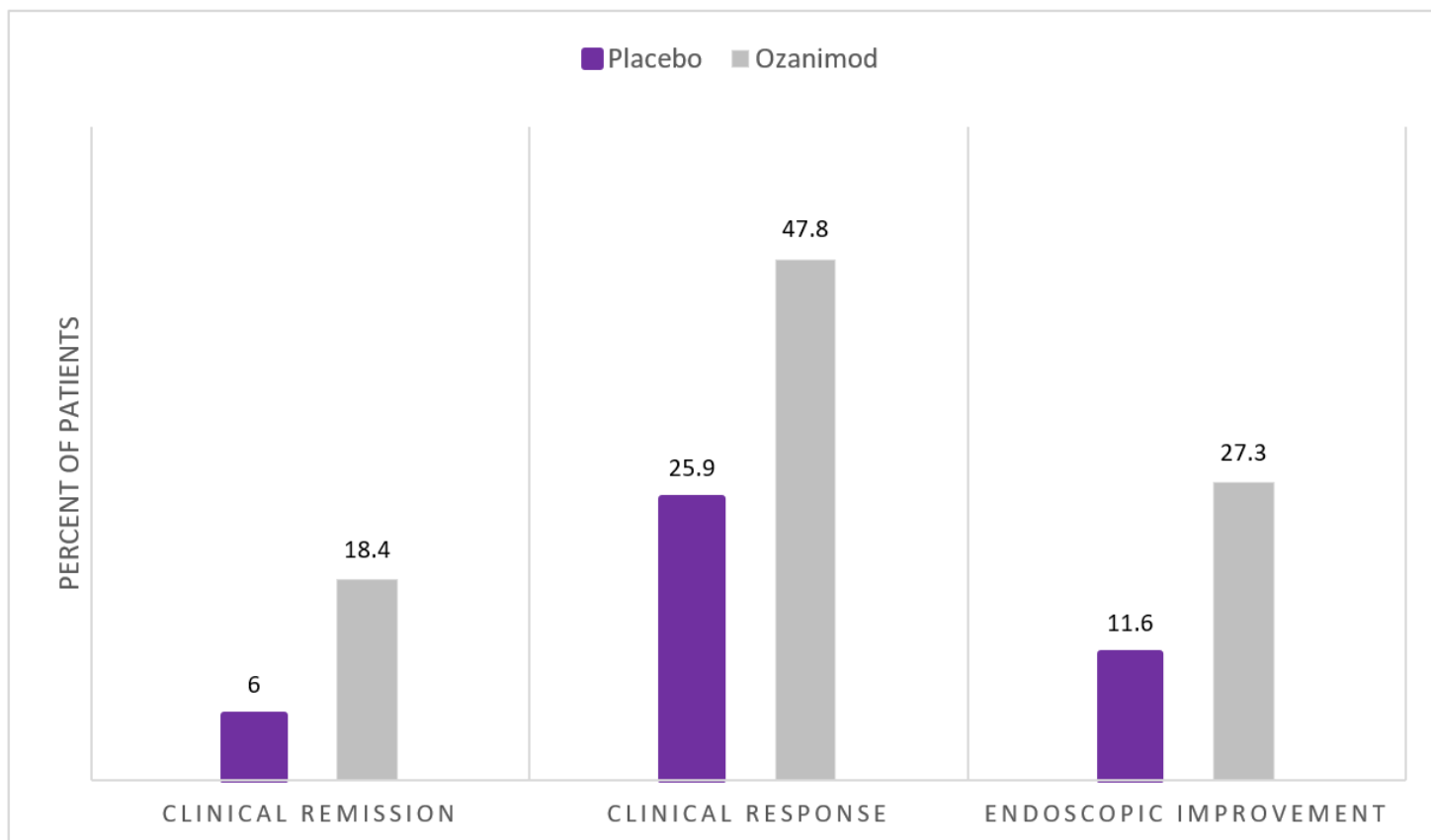


Figure 1: Induction of remission at week 10 and key secondary endpoints in True North.

Clinical Remission: 3-component Mayo score with rectal-bleeding subscore = 0; stool-frequency subscore ≤ 1 with a decrease of at least 1 from baseline; and endoscopy subscore ≤ 1 .

Clinical Response: reduction in total Mayo Score of 3 \geq points and $\geq 30\%$ from baseline or similar modification using 3-component Mayo Score.

COMMENTARY

Why Is This Important?

As discussed in prior summaries¹, multiple UC treatments have become available in the past 5 years. In addition to commonly used anti-TNF antibody treatments like infliximab (Remicade; Janssen Biotech, Horsham, PA) and adalimumab (Humira; AbbVie Biotechnology, Chicago, IL), anti-integrin antibody treatments like vedolizumab (Entyvio; Takeda Pharmaceuticals, Lexington, MA), anti-interleukin-12/23

antibodies such as ustekinumab (Stelara; Janssen Biotech), and selective JAK1 inhibitors like upadacitinib (Rinvoq; AbbVie Biotechnology) are FDA-approved for use. Given this expanding menu of therapies, new algorithms are needed to help gastroenterologists choose preferred treatment for individual UC patients by accounting for the strengths and limitations of individual agents.²

Although comparative RCTs are not available, upadacitinib, an oral selective JAK1 inhibitor with a relatively rapid onset of action, was superior for

induction of remission to other biologics and small molecules in 2 recent network meta-analyses.³⁻⁴ However, upadacitinib is approved for use only after inadequate response or intolerance to an anti-TNF agent.

Ozanimod is a selective sphingosine-1-phosphate receptor modulator, which leads to internalization of S1P1 receptors in lymphocytes and the prevention of lymphocyte mobilization to inflammatory sites and has also been used since 2020 for relapsing multiple sclerosis. Per the prescribing information, it's contraindicated in patients with major adverse cardiac events in the past 6 months, presence of second or third degree heart block, and severe sleep apnea. Elevation of liver transaminases, bradycardia, decreased lymphocyte counts, and macular edema are also risks. Therefore, it is suggested that patients should have complete blood count, ECG, LFTs prior to initiating therapy. Patients should be vaccinated against varicella-zoster virus or demonstrate antibodies to the virus prior to initiating treatment. In order to minimize the risk of bradycardia, patients should complete a 7-day titration by using 0.23mg daily for day 1-4, 0.46 mg daily for days 5-7, followed by increasing to standard dose of 0.92 mg daily.

Ultimately, Sandborn and colleagues should be commended for designing a methodologically rigorous RCT and getting study patients through a rigorous study protocol. Given the morbidity and mortality associated with moderate-

severe UC, the addition of ozanimod is welcome.

Key Study Findings

Clinical remission for moderately-severe UC patients was significantly more common with ozanimod 0.92 mg po qd vs placebo in both induction of

Caution

Ozanimod is contraindicated in patients with a recent history of major adverse cardiac events, history of heart block, or severe sleep apnea. LFTs and lymphocyte counts should be monitored, and the patient should be aware that it can increase the risk of macular edema, declines in pulmonary function, and herpes zoster infections despite vaccination.

My Practice

Our preferred use of ozanimod is for UC patients with moderate disease activity who prefer an oral agent and who do not have any of the risk factors for the above-mentioned contraindications. For example, we avoid ozanimod in UC patients with a history of uveitis. If patients are diabetic, then we routinely get an ophthalmologic exam before starting ozanimod. We avoid using it in patients with severe snoring, which may represent undiagnosed sleep apnea, and tend to avoid it in women of child-bearing age given the absence of data about its safety during pregnancy.

Ultimately, we individualize our care by reviewing risks and benefits of different therapies with each patient and conduct shared decision making.

Prior to prescribing ozanimod, we follow our standard protocol of recommending vaccination against multiple infections, including herpes zoster. In addition to baseline laboratory assessment (CBC, comprehensive metabolic profile) and ECG, we check carefully to ensure that there are not pre-existing cardiac conditions, sleep apnea or other pulmonary disease, or symptoms of uveitis. As part of our nutrition assessment, we also caution patients to limit intake of tyramine-rich foods (e.g., aged cheeses) since ozanimod-treated patients are at higher risk of side effects like hypertension if they consume more than 150 mg of tyramine.

For Future Research

Ongoing RCTs will define efficacy of ozanimod for Crohn's disease. Given the increasing number of available agents with different mechanisms of actions, comparative RCTs would be welcome to help establish positioning of therapies as well as longer-term safety data.

Conflict of Interest

Dr. Damas reports being an advisory board member for Janssen Pharmaceuticals, consultant for AbbVie Pharmaceuticals, and receiving research support from Pfizer Pharmaceuticals.

Dr. Schoenfeld reports no conflicts of interest.

Note: The authors of the True North study are active on Twitter. Tag them to discuss their work and this EBGI summary!

@silvio_silvio75

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Continuing Anti-TNF Agents Past 24 Weeks of Pregnancy Associated with Fewer IBD Relapses with No Increase in Adverse Fetal Outcomes

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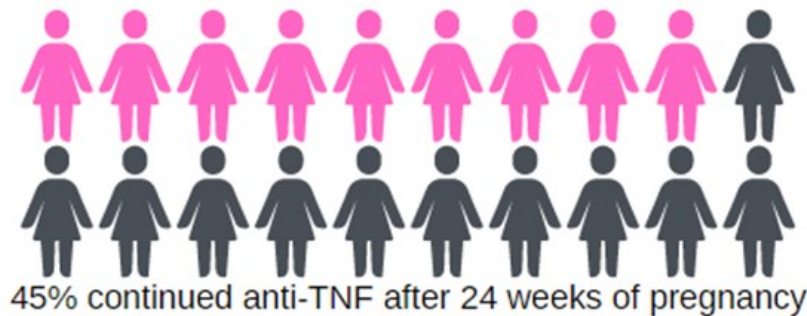
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This summary reviews Meyer A, Neumann A, Drouin J, et al. Benefits and Risks Associated With Continuation of Anti-Tumor Necrosis Factor After 24 Weeks of Pregnancy in Women With Inflammatory Bowel Disease: A Nationwide Emulation Trial. *Ann Intern Med.* 2022 Oct;175(10):1374-1382

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IBD and Pregnancy Outcomes in Pregnancies With Versus Without Anti-TNF Continuation After 24 Weeks of Pregnancy



Total of 5293 Pregnancies

- Lower risk of IBD relapse (aRR 0.93, CI 0.86-0.99)
- Lower risk of preterm birth (aRR 0.82, CI 0.68-0.99)
- NO increased risk of serious infections in offspring (aHR 1.09, CI 0.94-1.25)

STRUCTURED ABSTRACT

Question: Does continuing anti-TNFs beyond 24 weeks in pregnancy have an impact on maternal IBD relapse, adverse pregnancy outcomes, or serious infections in the offspring during the first 5 years?

Design: Retrospective, observational cohort study.

Setting: Nationwide population-based study using the French National Health data system (Système National des Données de Santé).

Patients: A total of 5,293 pregnancies with inflammatory bowel disease (IBD) between 2010 and 2020, with a prescribed anti-TNF (infliximab, adalimumab, golimumab, or certolizumab) between conception and 24 weeks of pregnancy. Median age of 29 years, with approximately 80% of patients with Crohn disease. Pregnancies exposed to methotrexate, vedolizumab, ustekinumab, or tofacitinib before 24 weeks were excluded.

Exposure: The “anti-TNF continue” group included any pregnancy with administration or a prescription of an anti-TNF (infliximab, adalimumab, golimumab, or certolizumab) after 24 weeks of gestation, whereas the “anti-TNF stop” group included pregnancies where anti-TNFs were not administered/prescribed beyond 24 weeks.

Outcomes: Three primary outcomes were maternal IBD relapse, adverse pregnancy outcomes, and serious infection in the offspring. IBD relapse was defined by at least 1 oral or rectal corticosteroid dispensing, IBD-related hospitalization, or surgery between 32 weeks and the end of pregnancy, or postpartum (within 6 months after delivery). Adverse pregnancy outcomes included pregnancy-related hospitalizations, cesarean section, stillbirth, prematurity (births before 37 weeks), and low (below tenth percentile) or large (above ninetieth percentile) birthweight. Serious infection in offspring was defined as any infection requiring hospitalization as the primary diagnosis. Children were followed from birth until onset of a serious infection, 5 years of life, or end of the study in December 2020.

Data Analysis: All pregnancies that occurred in women with IBD during the 11-year period were included in the analyses. A comparison of the risks for IBD relapse and adverse pregnancy outcomes between the 2 groups, anti-TNF continue and anti-TNF stop groups, was performed. A multivariate logistic regression model was used to predict risks and their ratios. A marginal Cox model with inverse probability weighting to compute hazard ratios was used to compare risk for serious infections in the offspring.

Funding: No private funding, done at the initiative of French National Health Service.

Results: Approximately 55% of pregnant women treated for IBD discontinued anti-TNF treatment before 24 weeks of pregnancy. Prescription of anti-TNF during pregnancy beyond 24 weeks of gestation was associated with less IBD relapse (adjusted rate ratio [aRR] 0.93, 95% confidence interval [CI] 0.86–0.99), a lower rate of prematurity (aRR 0.82, CI 0.68–0.99), and no difference in the overall rate of serious infections in the offspring (adjusted hazard ratio [aHR] 1.08, CI 0.94–1.25). (**Figure 1**) Importantly, 88.3% of women who had continued anti-TNF after 24 weeks of pregnancy were still treated with anti-TNF after 6 months of delivery, whereas only 71.1% of those who had stopped anti-TNF therapy before 24 weeks had it restarted. This study followed infants for risk of serious infections up to 5 years of age showing no increase in overall risk of infections throughout the first 5 years of the infants' life.

COMMENTARY

Why Is This Important?

Pregnant women with IBD are more likely to have pregnancy-related complications.¹ Studies have shown that women are likely to stop anti-TNF treatment during pregnancy, often on the recommendation of their physician, with discrepancy among the North American

and European guidelines on continuing anti-TNF therapy in late pregnancy.

North American IBD guidelines recommend continuing anti-TNF agents in pregnant IBD patients beyond 24 weeks.² However, previous European guidelines recommend stopping anti-TNF agents around week 24–26 of gestation to limit neonatal exposure, due to concerns about levels of inflix-

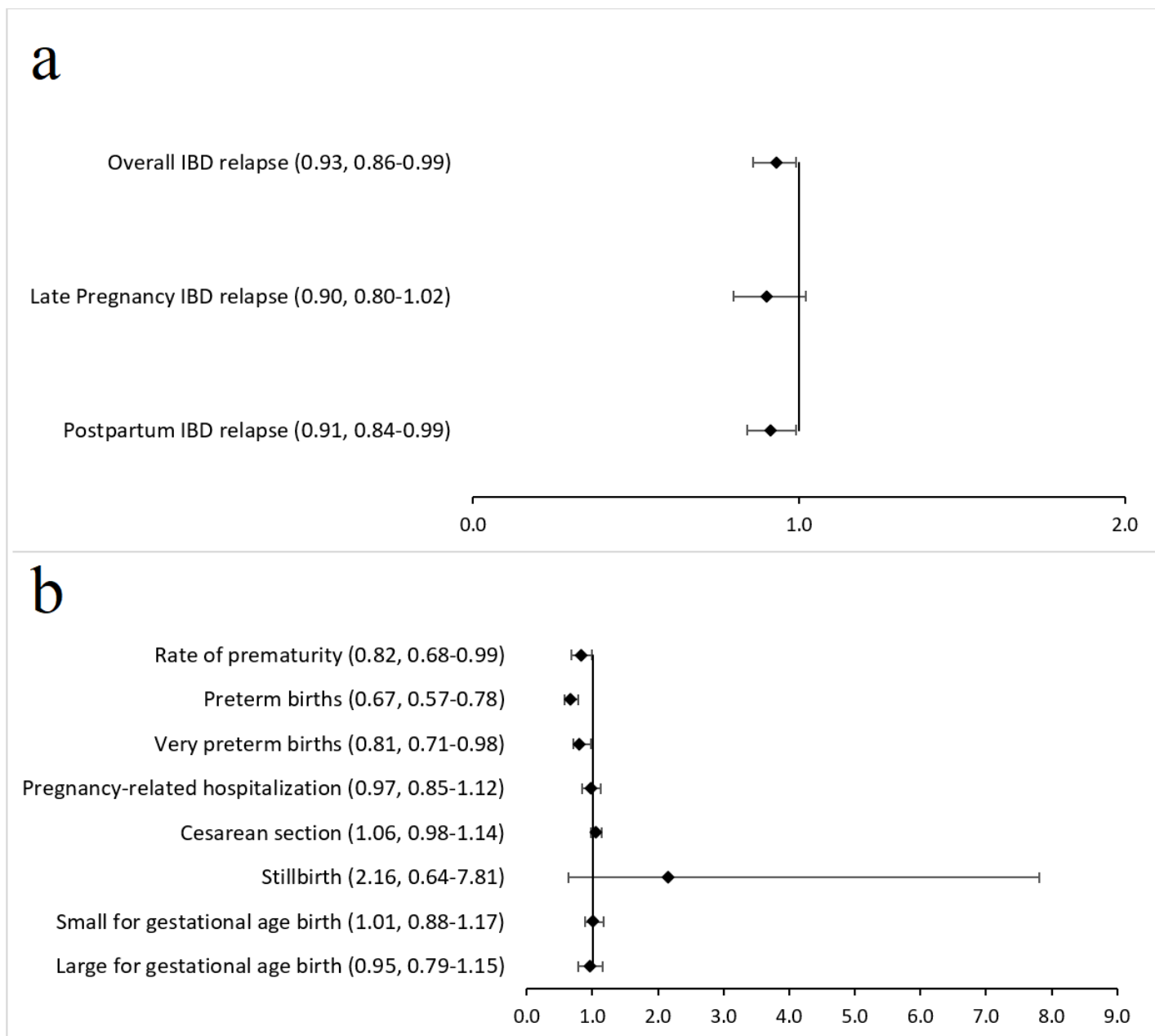


Figure 1: (a) IBD related outcomes. (b) Pregnancy related outcomes.
Adjusted rate ratio, 95% confidence interval.

mab and adalimumab in the fetus that can persist up to 7 months.³ Results from the recent PIANO study, a large prospective cohort study of 1,712 pregnant women with IBD on either no therapy, thiopurine, biologic, or combination therapy revealed no increase in adverse pregnancy or fetal outcomes in patients on therapy, how-

ever, higher disease activity in patients not on therapy was associated with worse outcomes⁴ These data are partly responsible for updated guidelines from the European Crohn's and Colitis Organisation, which now support continuing anti-TNF agents through the third trimester.⁵

Key Study Findings

This large study from France revealed that 55% of pregnant patients discontinued anti-TNF therapy after 24 weeks of gestation. Patients who continued anti-TNF therapy had better pregnancy outcomes overall, with lower IBD relapses and lower risk of premature births, without an increase in overall serious infections in infants up to 5 years of age.

Caution

This study was conducted using the French National Health data system, and algorithms rather than actual clinical data were used to identify patients with IBD, pregnancies, or serious infections. Drug administration was identified by either a dispensed prescription of a subcutaneous drug or facility administration of an infusion, however, subgroup analyses based on the infliximab group (administered in-hospital in France) yielded similar results. This study also evaluated only anti-TNF agents, and as such results cannot be generalized to non-anti-TNF biologics.

My Practice

Guided by the Toronto Consensus statement, the AGA care pathway, and evidence from the PIANO study, we discuss the overall safety of anti-TNF agents during pregnancy versus the risk

of active disease. We strongly counsel my patients based on available evidence to continue their biologic therapy through pregnancy. This study provides further evidence that the use of anti-TNF agents throughout pregnancy is not associated with worse outcomes, but rather lower disease relapse and risk of adverse pregnancy outcomes. We discuss with patients the importance of optimizing disease control prior to conception and throughout the pregnancy with emphasis on the importance of adequate disease control in late pregnancy to minimize adverse pregnancy outcomes for mother and child.

For Future Research

With the introduction and more widespread use of non-anti-TNF biologics and small molecules, we are faced with similar questions regarding the safety of these newer agents. Future research should focus on the safety of these medications during pregnancy and lactation as well as impact on response to vaccine and long-term risks of infection, immune-mediated disease, and other health outcomes. This will improve our shared decision making with patients regarding the use of these agents in IBD pregnancy—a high risk state with an increase in adverse maternal and fetal outcomes.

Conflicts of Interest

Dr. Abu-Heija and Dr. Schoenfeld report no potential conflicts of interest for this summary. Dr. Mahadevan reports being a consultant for AbbVie, Janssen, Takeda, Pfizer, Bristol Myers Squibb, Boehringer Ingelheim, Protagonist, Prometheus Biosciences, Rani Therapeutics, Surrozen, Gilead, and Eli Lilly.

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Donor Stool Product for FMT Decreases Recurrent *Clostridioides difficile* Infection: RBX2660 Is the First FDA-Approved Live Biotherapeutic Product



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This summary reviews Khanna S, Assi M, Lee C et al. Efficacy and Safety of RBX2660 in PUNCH CD3, a Phase III, Randomized, Double-Blind, Placebo-Controlled Trial with a Bayesian Primary Analysis for the Prevention of Recurrent *Clostridioides difficile* Infection. *Drugs* 2022; **82**: 1527–38.

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STRUCTURED ABSTRACT

Question: Is RBX2660 (Rebyota; Ferring Pharmaceutical, Parsippany, NJ), an enema consisting of full-spectrum donor stool microbes for fecal microbiota transplant (FMT), superior to placebo to reduce recurrent *Clostridioides difficile* infection (rCDI)?

Design: Phase III, multi-center, double-blind, placebo-controlled randomized controlled trial (RCT; PUNCH CD3), with a Bayesian primary analysis integrating data from a prior phase IIb RCT with similar design (PUNCH CD2).¹

Setting: Forty-four sites in the US and Canada.

Patients: Included patients were ≥ 18 years old and had rCDI (≥ 1 recurrences after a primary CDI) or had ≥ 2 hospitalizations with severe CDI within the past 12 months and had completed one or more courses of standard-of-care antibiotic therapy. Eligible patients were required to

demonstrate a positive stool test for *C. difficile* toxin gene by polymerase chain reaction (PCR), enzyme immunoassay (EIA) for *C. difficile* toxin, or other assay within 30 days of enrollment in the trial. Multiple exclusion criteria included, but were not limited to, known history of inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), celiac disease, and prior FMT.

Interventions/Exposure: Eligible patients were randomized 2:1 to RBX2660 or normal saline placebo, which was administered rectally as a single dose. The 150 ml enema was administered at the study site after the patient had completed standard-of-care antibiotic therapy plus a 24–72-hour washout period. The washout period did not include any bowel preparation prior to enema administration.

Outcome: The primary endpoint was absence of CDI diarrhea within 8 weeks of enema administration, which was defined as treatment success. The secondary endpoint was absence of CDI diarrhea within 8 weeks plus no new CDI episodes through 6 months after administration of enema, which was defined as sustained clinical response. For patients with treatment failure, open-label treatment with RBX2660 was offered.

Data Analysis: Modified intention-to-treat (mITT) analysis, defined as all randomized patients who completed treatment and 8 weeks of follow-up, was performed for the primary and secondary endpoints. In addition, a Bayesian hierarchical model* that utilized data from the dose-finding, placebo-controlled, phase IIb RCT (PUNCH CD2) was conducted. In PUNCH CD2, patients were randomized 1:1:1 to receive 2 treatment doses separated by 1 week: RBX2660 followed by another dose of RBX2660, RBX2660 followed by placebo, or placebo followed by placebo.¹ Only the 1-dose RBX2660 group and the placebo group were utilized in the Bayesian analysis.

Funding: Rebiotix, a Ferring Company, and manufacturer of RBX2660.

Results: From July 2017 through February 2020, 262 patients (n = 177 for RBX2660 and n = 85 for placebo) comprised the mITT analysis: median age 63.0 (range 19-93), 68.5% female; 92.1% White; 88.0% received vancomycin alone as standard-of-care antibiotic therapy; 73.0% used PCR and 24.7% used EIA for CDI confirmation; and 36.3% had > 3 CDI episodes prior to enrollment.

In the mITT analysis for the PUNCH CD3 population, treatment success, defined as absence of CDI-associated diarrhea at 8 weeks, occurred more commonly in the RBX2660 group vs placebo: 71.2% vs 62.4%. In the PUNCH CD2 trial, 1-dose of RBX2660 (n = 44) was superior to placebo (n = 44) for treatment success (66.7% vs 45.4%, $P= 0.048$). Using the FDA-recommended approach to borrowing data from PUNCH CD2 and applying the Bayesian hierarchical model, the mITT analysis again showed treatment success occurred more commonly in the RBX2660 group vs placebo: 70.6% vs 57.5% with a posterior probability of success of 0.991 (i.e., 99.1% probability that RBX2660 is superior to placebo for treatment success).

Among study patients who achieved treatment success, rCDI was infrequent at 6 months in both RBX2660 (7.9%) and placebo (8.4%) (**Figure**). Sixty-five patients had treatment failure and received open-label RBX2660. In this extension study, 62.5% of patients who had originally received placebo and 53.7% of patients who had originally received RBX 2660 achieved treatment success after getting the open-label course of treatment. No severe adverse events related to study treatment or rectal administration occurred. GI adverse events, including abdominal discomfort and diarrhea, were the only adverse events reported in more than 5% of participants in all treatment groups.

NOTE

*Originally, 2 Phase III RCTs were planned. However, during PUNCH CD3, the study investigators noted challenges with patient recruitment (e.g., patients may be less likely to enroll in a placebo-controlled RCT when FMT for rCDI was already available as an experimental procedure under FDA's enforcement discretion policy). After consultation with the FDA, the data analysis plan utilizing a Bayesian hierarchical model and PUNCH CD2 data in lieu of a second Phase III RCT was agreed upon. A complete discussion of Bayesian analysis is beyond the scope of this summary. The key components of Bayesian analysis are that it allows the incorporation of prior data (e.g., PUNCH CD2 data) and provides a posterior probability statement (e.g., what is the probability that RBX2660 is superior to placebo for achieving treatment success?).

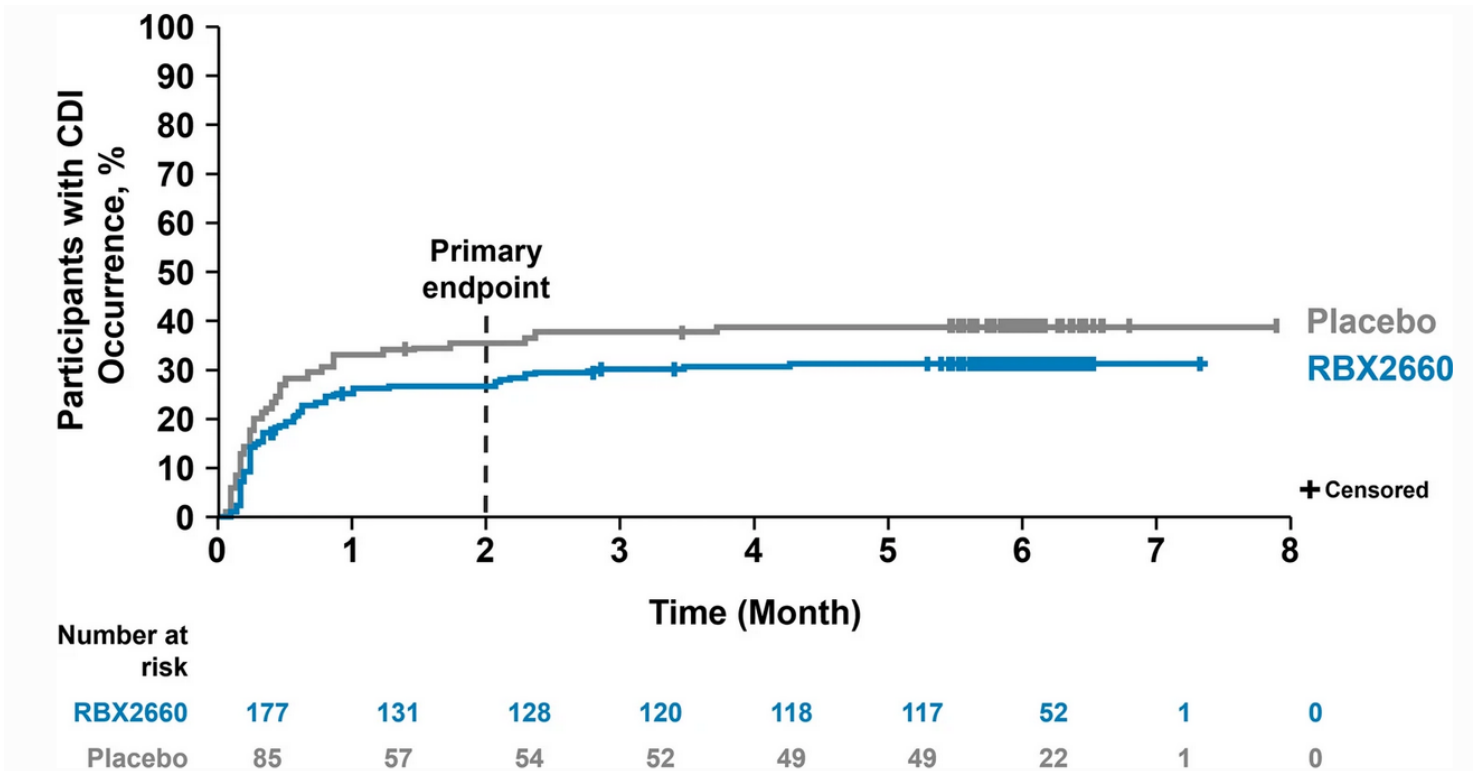


Figure 1: Kaplan-Meier analysis of time to recurrent *Clostridioides difficile* infection (CDI), modified intent-to-treat population. Primary endpoint is treatment success, which is defined as absence of CDI-associated diarrhea within 8 weeks of treatment.

COMMENTARY

Why Is This Important?

FMT has demonstrated effectiveness for the prevention of rCDI, and is currently recommended in guidelines from the American College of Gastroenterology and the Infectious Diseases Society of America.^{2,3} However, prior to the very recent approval of RBX2660, there were no FDA-approved FMT products and the procedure could only be performed under the agency's policy of enforcement discretion.^{1,4-5} Since 2013, stool banks, such as OpenBiome, which centralize donor screening and testing to reduce risk of infection transmission, have provided most donor fecal material for FMT. However, given the FDA's designation of donor stool as a biologic drug, there is no mechanism to regulate

stool banks. The cost of donor material is not covered by insurance and patient access is limited as the supply of stool bank material is primarily reserved for centers of excellence. As of November 30, 2022, RBX2660 becomes the first FDA-approved source of donor stool for FMT to prevent rCDI.

RBX2660 contains the full spectrum of fecal microbes gathered from healthy donors. The stool is screened for multiple pathogens then processed to a stable cryopreserved liquid suspension. Per prescribing information, the cryopreserved liquid suspension is thawed and then administered as an enema⁶. The 150 ml enema relies on gravity for infusion of contents over 10-15 minutes with the patient in the left lateral decubitus position or a prone knee-chest

position, and patients remain in position for an additional 15 minutes after the enema has been completely administered.

As discussed previously in *Evidence-Based GI*,⁴⁻⁵ the FDA is currently reviewing other live biotherapeutic products for treatment of rCDI. Specifically, SER-109 is currently under FDA review with comment due in the second quarter of 2023. SER-109 consists of capsules of donor-derived, live purified Firmicutes bacterial spores, administered orally for 3 consecutive days. In its Phase III, double-blind, placebo-controlled RCT, ECOSPOR III, it was superior to placebo for preventing rCDI: 88% vs 60%.

Key Study Findings

Treatment success, defined as absence of CDI diarrhea at 8 weeks, occurred more commonly in the RBX2660 group vs placebo: 71.2% vs 62.4%. Sustained clinical response was also high: rCDI at 6 months occurred in only 7.9% of RBX2660 and 8.4% of placebo-treated patients who achieved cure at 8 weeks (**Figure 1**).

Caution

Although comparative RCTs are not available, FMT administered by colonoscopy and oral capsules, including SER-109, have reported treatment success in the 90% range. It's unclear whether differences in study design or use of an enema to administer RBX2660 may have impacted treatment

success rates with RBX2660. Furthermore, due to strict enrollment criteria and exclusion of patients with IBD, IBS, and other conditions, the patients enrolled in PUNCH CD3 may not represent the real-world population of patients with rCDI.

There are several study design issues that might have impacted results. Most cases of rCDI used PCR to confirm presence of *C. difficile* (73.0%) as opposed to requiring all study patients to have a positive EIA for *C. difficile* toxin. Since colonization is common and can persist for months after a CDI, some patients testing positive by PCR at the study onset may have been at low risk for rCDI and diarrhea within 8 weeks. Alternatively, during 8-week follow-up, some patients may have had functional diarrhea and false positive PCR for *C. difficile* and been miscategorized as treatment failure. Furthermore, no washout of antibiotics from the colon with an osmotic laxative or bowel preparation was performed prior to the enema administration of RBX2660, so it's possible that residual antibiotics could have reduced colonization by the donor microbiota released by enema-administration of RBX2660 and decreased its efficacy.

My Practice

RBX2660 will be commercially available in the US shortly and will be the most accessible treatment option for patients with rCDI after they have completed standard-of-care antibiotic therapy and will reserve it for patients with their third episode of *C. difficile* (i.e.,

initial episode plus 2 recurrences). I'll follow the prescribing information for administering the enema formulation of RBX2660. It is not yet clear that office-based administration of fecal enemas will be required. I'll treat most patients after a 72-hour washout period and administer magnesium citrate one day before RBX2660 administration to minimize residual antibiotics in the colon which might reduce the efficacy of RBX2660. I anticipate the biggest challenge will be insurance coverage and cost to patients, particularly when up to 30% of patients may require repeat dosing. Stool banks operating under investigational new drug status will continue to have a role, providing donor stool for FMT in patients who cannot access commercial formulations or who fail to achieve cure after RBX2660. If SER-109 or other FDA-approved live biotherapeutic products become available, I'll reassess my practice.

For Future Research

Given the high effectiveness of FMT and the greater availability of safe donor products, future studies should look at utilizing FMT earlier in the disease cycle, perhaps after a first or second episode, especially in patients who had a severe CDI or who are at high risk of further recurrence. Use of FMT in the acute setting to treat severe/fulminant CDI is another indication which needs further study. Real-world effectiveness in subpopulations who were excluded from industry trials, such as children and patients with IBD, will be important to understand. Finally, as new pathogens

emerge, it will be important to improve and rapidly update donor screening protocols to optimize patient safety. Surveillance studies for potential safety concerns, including both infectious agents and unforeseen consequences of manipulating the gut microbiome, will continue to be important.

Conflict of Interest

Dr. Schoenfeld reports no potential conflicts of interest. Dr. Kelly reports serving as a consultant for Sebelo Pharmaceuticals and is a volunteer clinical advisor for Openbiome.

Note: The authors of this article are active on social media. Tag them on Twitter discuss this EBGI summary and their other work.

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NSAID Use and the Risk of IBD Exacerbations: Fact or Fiction?



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This summary reviews: Cohen-Mekelburg S, Tony V, Wallace B et al. The Association Between Nonsteroidal Anti-Inflammatory Drug Use and Inflammatory Bowel Disease Exacerbations: A True Association or Residual Bias? *Am J Gastroenterol.* 2022 Nov 1;117(11):1851-1857.

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STRUCTURED ABSTRACT

Question: Does the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with inflammatory bowel diseases (IBD) increase the risk of exacerbations?

Setting: This retrospective study was performed using data from patients with IBD in the Veterans Affairs (VA) Corporate Data Warehouse between January 1, 2004, to September 30, 2015.

Participants: An initial analysis cohort of patients with Crohn's disease and ulcerative colitis was created using an algorithm of *International Classification of Diseases, Ninth Revision (ICD-9)* codes which required at least 2 clinical encounters for IBD with at least 1 being an outpatient visit.

Intervention/Exposure: NSAID exposure was the primary independent variable, and this was identified using outpatient pharmacy files based on dispense date. Aspirin and acetaminophen exposures were not included.

Outcomes: The primary outcome was IBD exacerbation defined as any outpatient IBD-related corticosteroid prescription requiring at least a 1-week supply without a non-IBD indication in the week preceding the date the corticosteroid prescription was filled. This allowed maximization of specificity in the ascertainment of an IBD flare.

Data Analysis: IBD patients with NSAID exposure were matched 1:1 to those without NSAID exposure based on preselected potential confounders including age, gender, race, Charlson comorbidity score, smoking status, IBD type, use of immunomodulator or biologic medications. The association between NSAID exposure and time to IBD flare in this matched cohort was assessed using a Cox proportional hazards model. Only the first exacerbation after NSAID use was studied. To evaluate for residual confounding, a previous event rate ratio was computed. To assess for within-person confounding, a self-controlled case series analysis was performed to estimate incidence rate ratios of IBD flares at a predetermined time range of hypothesized excess risk (6 months after NSAID exposure) compared to a pre-exposure time frame (1-year preceding NSAID exposure), but only in the cohort of patients that experienced an IBD flare after NSAID exposure.

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Results: An analysis cohort of 35,031 patients was created after matching 15,705 patients with NSAID exposure to 19,326 patients without NSAID exposure. Most patients were male (93.2%) and White (88.8%). The

mean follow-up was 5.9 years. Patients exposed to NSAID were more likely younger (57.1 vs 61.9 years, $P < 0.001$) and female (91.4% vs 94.6%, $P < 0.001$). Patients with IBD exposed to NSAID had a higher likelihood of IBD exacerbation compared to the unexposed (Hazard ratio [HR] 1.24; 95% confidence interval [CI] 1.16-1.33). However, the likelihood of an IBD exacerbation before NSAID exposure was 1.3 (95% CI 1.21-1.39) in the NSAID-exposed group vs the unexposed. As such, the computed previous event rate ratio of 0.95 (95% CI 0.89-1.01) raised the possibility of residual confounding.

The case series analyses of 3,968 patients with NSAID exposure that had at least 1 IBD flare-up showed an incidence rate ratio of 1.95 (95% CI 1.79-2.15) in the 1 year before NSAID exposure, 6.27 (95% CI 5.15-7.63) in the 0-to-2-week transition period following exposure, 1.77 (95% CI 1.37-1.43) in the 2 to 6 week post-NSAID dispense date, and 1.24 (95% CI 1.07-1.43) in the 6 weeks to 6 months post-NSAID dispense date. A sensitivity analysis using an alternative pre-exposure period of 1-month preceding NSAID dispense date was performed to assess for robustness of the initial case series analyses assumptions. A similar trend in incidence rate ratios was observed.

COMMENTARY

Why Is This Important?

In large studies of patients with IBD, as much as 60% report abdominal pain¹, a rate that is higher than in the general population.^{2, 3} Abdominal pain is a hallmark presentation of IBD exacerbations, but it remains undertreated because of the concern that the use of analgesics (including NSAIDs and opiates) may exacerbate symptoms or mask a relapse.⁴ As such, despite the anti-inflammatory and analgesic properties of NSAIDs, many providers avoid them in patients with IBD exacerbations. Cohen-Mekelburg et al perform a retro-

spective multimethod analysis using VA data to investigate the association between NSAID use and IBD exacerbations. They utilize analytical methods aimed at minimizing the effects of residual confounding and reverse causality or protopathic bias in database studies (e.g., NSAIDs are prescribed for abdominal pain related to early IBD exacerbation, so it is the IBD exacerbation that causes the medicine to be prescribed, leading to an overestimate of the risk of IBD exacerbation with NSAID use in epidemiologic studies). This has been a major limitation of similar studies in the past.

		Adjusted Hazard Ratio	95% CI
Post-NSAID exposure analysis	Likelihood of IBD exacerbation (NSAID exposed vs NSAID unexposed)	1.24	1.16-1.33
Pre-NSAID exposure analysis	Likelihood of IBD exacerbation (NSAID exposed vs NSAID unexposed)	1.3	1.21-1.39
		Overall incidence rate ratio	95% CI
Self-controlled case series	1-year pre-NSAID dispense date	1.95	1.76-2.15
	0–2-week post NSAID dispense date	6.27	5.15-7.63
	2–6-week post NSAID dispense date	1.77	1.37-1.43
	6 week-6-month post NSAID dispense date	1.24	1.07-1.43

Table 1. Results of a Cox proportional hazards model on the likelihood of IBD exacerbation before and after NSAID exposure, and self-controlled case series.

CI, confidence interval; IBD, inflammatory bowel disease; NSAID, nonsteroidal anti-inflammatory drugs.

Key Study Findings

While the authors show an increased risk of IBD exacerbations following NSAID exposure, they also observed that the overall likelihood of IBD exacerbation before NSAID exposure was also greater in the NSAID-exposed cohort (**Table 1**).

Their “previous event rate ratio” of 0.95 suggests that this finding may be independent of NSAID exposure and more likely from an increased likelihood of IBD exacerbation in NSAID-exposed patients that precedes exposure to NSAID. This observation was further substantiated by the fact that in the self-controlled case series, the risk of IBD did not significantly increase in the 2 weeks to 6 months after NSAID exposure.

Caution

The major strengths of this study are the analytical methods used to control for reverse causality and minimize residual confounding. However, the study is limited by the difficulty generalizing the results which were obtained using VA data. Unsurprisingly, their analysis cohort was made up of 93% men, 89% White, with a mean age of 60 years. Despite this, they found that NSAID exposure was higher among younger patients and females which could suggest that different results could be seen in a younger population with more women. The authors also allude to the limited availability of details on IBD history including phenotype and duration of disease. Importantly, because NSAID can be obtained without a prescription, it can be difficult to account for their use outside the VA system which can lead to misclassification bias. The authors

also did not investigate the outcome of GI bleeding which may accompany IBD exacerbations and could be impacted by NSAID use. Even with these limitations, this study provides some of the best evidence addressing a very important issue in the care of patients with IBD.

My Practice

In my practice, we tend to avoid NSAID in hospitalized patients with IBD exacerbations. This is because even though these patients may present with pain, they may also present with concurrent gastrointestinal bleeding. In addition, hospitalization affords the timely administration of IV steroids which leads to improvement in pain. The findings of this study may have a bigger impact on the outpatient management of day-to-day non-IBD pain as it does provide some reassurance for healthcare providers to prescribe NSAID for analgesia. Given these data, the risk of NSAID use in IBD patients is likely outweighed by the benefit if there is an appropriate reason for short-term use and it's preferable to avoid opioids in these patients.

For Future Research

It is important to validate these findings in a population outside the VA, preferably one that is younger, and consists of a larger proportion of women which will allow for secondary generalizability. It would also be important to study outcomes such as gastrointestinal bleeding especially because of the increased risk of gastric ulcers in patients on concurrent NSAID

and corticosteroids.

Conflict of Interest

Dr. Philip Okafor reports no potential conflicts of interest.

Note: The authors of this article are active on Twitter. Tag them to discuss their work and this EBGI summary.

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