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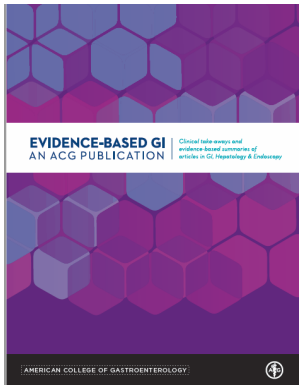

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Evidence-Based GI **Volume 2, Issue 8**

October 2022

TABLE OF CONTENTS

EVIDENCE-BASED GI
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Upadacitinib, a Selective JAK1 Inhibitor, for Moderate-Severe Ulcerative Colitis: Adjusting the Top-Down Treatment Algorithm for UC

Dr Jami Kinnucan
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Dr. Philip Schoenfeld
Editor-in-Chief

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This summary reviews: Danese S, Vermeire S, Zhou W, et al. Upadacitinib as Induction and Maintenance Therapy for Moderately to Severely Active Ulcerative Colitis: Results from Three Phase 3, Multicentre, Double-Blind, Randomised Trials. Lancet 2022; 399: 2113-28. https://pubmed.ncbi.nlm.nih.gov/35644166/

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STRUCTURED ABSTRACT

Question: Is upadacitinib (Rinvoq), a selective JAK1 inhibitor, superior to placebo for induction and maintenance of remission in moderately to severely active ulcerative colitis (UC)?

Design: To assess induction of remission at 8 weeks, 2 multicenter, double-blind, placebo-controlled randomized controlled trials (RCTs; U-ACHIEVE substudy 2 and U-ACCOMPLISH) were conducted, and a single multi-center, double-blind, placebo controlled RCT (U-ACHIEVE substudy 3) was performed to assess maintenance of remission at 52 weeks. Randomization stratified for multiple factors, including history of biologic failure, baseline corticosteroid use, and baseline Adapted Mayo Score ($\leq$7 vs >7).

Setting: Each RCT was conducted in approximately 200 centers in 35-40 countries across Europe, North and South America, Australasia, Africa and

the Asia-Pacific region.

Patients: In the induction of remission RCTs, patients were: (a) 18-75 years old; (b) confirmed UC diagnosis ≥ 90 days; (c) moderate-severe UC based on Adapted Mayo Score of 5-9 with endoscopic subscore of 2-3; and (d) previous inadequate response/loss of response/intolerance to standard UC treatment with 5-ASA, steroid, immunosuppressant, or biologic therapy. Exclusion criteria included active infection, toxic megacolon or prior exposure to JAK inhibitors. Patients who achieved clinical remission after 8 weeks of upadacitinib treatment were eligible for enrollment in the maintenance of remission RCT.

Interventions/Exposure: In the 2 induction of remission RCTs, patients were randomized 2:1 to upadacitinib 45 mg po qd vs placebo for 8 weeks. In the maintenance of remission RCT, patients were randomized 1:1:1 to upadacitinib 30 mg po qd, upadacitinib 15 mg po qd, or placebo for 52 weeks.

Outcome: The primary endpoint was clinical remission defined as Adapted Mayo score ≤ 2 with stool frequency score ≤ 1 and not greater than baseline, rectal bleeding score = 0, and endoscopic subscore ≤ 1 without friability*. Multiple secondary endpoints were assessed, including endoscopic remission and clinical response defined as decrease in Adapted Mayo Score of ≥ 2 points and ≥ 30% from baseline with decrease in rectal bleeding score of ≥ 1 point. In addition to standard safety analyses, pre-specified adverse events of interest were serious infection, herpes zoster, malignancy, major adverse cardiac events (MACE), and venous thromboembolisms.

Data Analysis: Modified intention-to-treat analysis defined as patients who were randomized and received at least one dose of study medication was performed for the primary and secondary endpoints in the induction RCTs. Safety analysis performed for any patient who received study medication in both induction and maintenance RCTs.

Funding: AbbVie Pharmaceuticals.

*_____

Note: the Adapted Mayo Score assesses rectal bleeding score (0-3), stool frequency score (0-3), and centrally-assessed endoscopy subscore (0-3), but excludes the Physician's Global Assessment used in the full Mayo score. Therefore, the score range is 0-9 with 9 representing most severe UC.

Results: From approximately October 2018 through January 2021, 988 patients were enrolled and included in efficacy analysis. Patient characteristics included male: 61-63%, mean age: 40-45 years old, mean disease duration: 4.9-6.6 years, Adapted Mayo Score at baseline > 7 = 39-41%, left-sided UC: 48-51%, and prior biologic therapy failure: 50%-53%.

Clinical remission was significantly more common with upadacitinib 45 mg qd vs placebo in both induction of remission RCTs: 26% vs 5% and 34% vs 4%, respectively (Table 1a-b), and maintenance of remission was more common with upadacitinib 30 mg and upadacitinib 15 mg vs placebo: 52% and 42% vs 12%, respectively (**Figure 1**).

Upadacitinib treatment was superior to placebo for all secondary endpoints in the induction of remission and maintenance of remission RCTs. Frequency of serious infections were similar in the upadacitinib and placebo groups in the 8-week induction of remission RCTs (1-2%) and in the 52-week maintenance of remission RCT (3-4%). No GI perforations or MACE occurred in the upadacitinib groups, although these did occur in placebo groups. Herpes zoster occurred in upadacitinib-treated patients in the induction of remission RCTs (n = 3) and in maintenance of remission RCT (n = 12).

Editor's Note: Although these 3 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.

Outcome (%)	Upadacitinib 45mg po qd (n=319)	Placebo (n= 154)	Adjusted Treatment Difference (95% CI)
Clinical Remission*	26%	5%	21.6% (15.8%-27.4%)
Endoscopic Remission	14%	1%	12.7% (8.4%-17.0%))
Clinical Response**	73%	27%	46.3% (38.4%-54.2%)

Table 1a. Induction of remission at week 8 in U-ACHIEVE substudy 2

*Clinical Remission: Adapted Mayo score $\leq$ 2 with stool frequency score $\leq$ 1 and not greater than baseline, rectal bleeding score = 0, and endoscopic subscore $\leq$ 1 without friability.

**Clinical Response: Decrease in Adapted Mayo Score of $\geq$ 2 points and $\geq$ 30% from baseline with decrease in rectal bleeding score of $\geq$ 1 point.

Outcome (%)	Upadacitinib 45mg po qd (n=341)	Placebo (n= 174)	Adjusted Treatment Difference (95% CI)
Clinical Remission*	33%	4%	29.0% (23.2%-34.7%)
Endoscopic Remission	18%	2%	15.9% (11.4%-20.3%)
Clinical Response**	74%	25%	49.4% (41.7%-57.1%)

Table 1b. Induction of remission at week 8 in U-ACCOMPLISH

*Clinical Remission: Adapted Mayo score ≤ 2 with stool frequency score ≤ 1 and not greater than baseline, rectal bleeding score = 0, and endoscopic subscore ≤ 1 without friability.

**Clinical Response: Decrease in Adapted Mayo Score of ≥ 2 points and ≥ 30% from baseline with decrease in rectal bleeding score of ≥ 1 point.

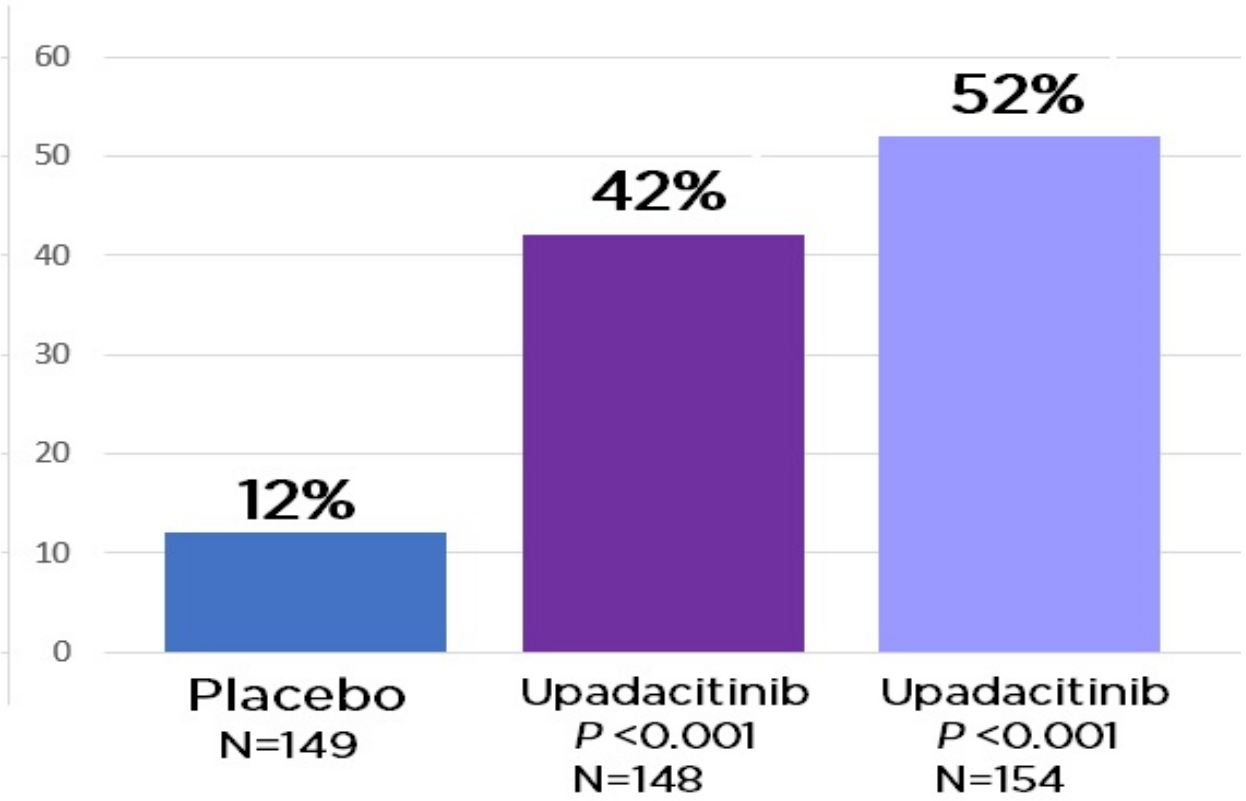

Figure 1. Maintenance of Remission at Week 52

COMMENTARY

Why Is This Important?

There is an expanding landscape of therapies for UC treatment. Available biological therapies include anti-tumor necrosis factor (TNF) antibody treatments like infliximab (Remicade), adalimumab (Humira), golimumab (Simponi), and anti-integrin antibody treatments like vedolizumab (Entyvio) and anti-interleukin-12/23 antibodies such as ustekinumab (Stelara). Recently, small molecule therapies have also been approved for moderate-severe UC, including sphingosine-1 phosphate inhibitors like ozanimod (Zeposia) and non-selective janus kinase (JAK)

inhibitors including tofacinitinib (Xeljanz). Given this expanding menu of therapies, new algorithms are sorely needed to account for the strengths and limitations of these agents and to help gastroenterologists choose the optimal treatment for individual UC patients.

Upadacitinib, a selective JAK1 inhibitor, offers many potential advantages for treating UC.[1] First and foremost, it's quite effective with large absolute increases in clinical remission rates vs placebo after 8 weeks of induction therapy and after 52 weeks of maintenance therapy. Although comparative RCTs are not available, this magnitude of benefit was superior to other biologics and small molecules in 2 recent network meta-analyses.[2-3] It's an oral agent taken once daily, which may be preferable for some patients, and this class of agents has a relatively rapid onset of action.[4] As a more selective JAK1 inhibitor, it may minimize toxicities associated with pan-JAK blockade. However, the Food and Drug Administration (FDA) only approved upadacitinib for UC treatment AFTER inadequate response or intolerance to an anti-TNF agent, which is similar to the labelling for tofacitinib for UC, largely due to safety concerns raised in post-marketing safety studies of tofacinitib plus methotrexate in older rheumatoid arthritis patients with cardiovascular risks.

Safety is very important with any new class of drugs, but some context is also important. Safety concerns primarily arose from a planned, post-authorization, safety RCT where tofacitinib was compared to anti-TNF agents in rheumatoid arthritis patients aged $\geq$ 50 years old with at least one cardiovascular risk factor and on background methotrexate with median follow-up of 4 years. Cancers and MACE were numerically higher with tofacitinib and did not meet non-inferiority criteria.[5] Interim analysis also demonstrated an increased risk for venous thromboembolisms in patients with tofacitinib 10 mg bid (vs tofacitinib 5 mg bid or anti-TNF treatment), although overall incidence was low. The incidence of MACE was lower in the tofacitinib UC trials, and no MACE occurred in upadacitinib-treated patients in the induction or maintenance of remission RCTs. Upadacitinib selectively targets JAK1 inhibition and minimizes JAK2 inhibition, which is the kinase whose inhibition is associated with increased platelet count and thrombosis, so the safety of upadacitinib in younger UC patients may differ. Additional safety data from open-label extension trials are forthcoming.

Ultimately, Danese and colleagues are to be congratulated for producing outstanding RCTs as well as completing patient enrollment during the COVID-19 pandemic and getting study patients through a rigorous study protocol. Although the multitude of available UC treatments may create confusion in the treatment algorithm, there is undoubtedly an unmet medical need for many UC patients that will be addressed with

upadacitinib.

Key Study Findings

Clinical remission was significantly more common with upadacitinib 45 mg qd vs placebo in both induction RCTs: 26% vs 5% and 34% vs 4%, respectively, and maintenance of remission was more common with upadacitinib 30 mg and upadacitinib 15 mg vs placebo: 52% and 42% vs 12%, respectively.

Caution

Per FDA prescribing information, upadacitinib is limited to "adults with moderately to severely active ulcerative colitis who have had an inadequate response or intolerance to one or more TNF blockers." In addition to safety concerns noted above with tofacitinib, a non-selective JAK inhibitor, an increased risk of herpes zoster and cytomegalovirus infection may occur with upadacitinib, and there is inadequate data to determine safety of all small molecule agents during pregnancy.

My Practice

Given the rapid expansion of biologics and small molecule agents to treat moderate to severe UC in the past 5 years, our approach to managing these patients continues to evolve. Our use of upadacitinib is limited to patients who have had an inadequate response or intolerance to at least one anti-TNF therapies. It's advantageous to have an oral agent with rapid durable response with lack of immunogenicity concerns for these individuals. Therefore, we individualize our approach to patient care by reviewing risks and benefits and conduct shared decision making. If a JAK inhibitor is used, we'll use either tofacitinib or upadacitinib based on insurance coverage. Anecdotally, we've found insurance coverage for upadacitinib quite good recently.

Prior to prescribing upadacitinib, we follow our standard protocol of recommending vaccination against multiple infections, including herpes zoster. In addition to baseline laboratory assessment (CBC, comprehensive metabolic profile), we check lipid parameters and do follow-up lipids at 12 weeks, which is recommended in the FDA prescribing information due to the potential for increases with low-density lipoproteins, high-density lipoprotein, and total cholesterol.

For Future Research

Ongoing RCTs will define efficacy of upadacitinib 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. Kinnucan reports serving as a

consultant/advisory board member for Janssen Pharmaceuticals, Pfizer Pharmaceuticals, AbbVie Pharmaceuticals, Takeda Pharmaceuticals, and Bristol Myers Squibb Pharmaceuticals. Dr. Schoenfeld reports no conflicts of interest.

Note: The authors of the article published in *Lancet* are active on social media. Tag the to discuss their work and this EBGi summary!

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Colonoscopy Reduces CRC Incidence and CRC-Related Morality…If You Get It!

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This summary reviews: Bretthauer M, Løberg M, Wieszczy P, et al. Effect of Colonoscopy Screening on Risks of Colorectal Cancer and Related Death. New England Journal of Medicine Oct 9, 2022. https://pubmed.ncbi.nlm.nih.gov/36214590/

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STRUCTURED ABSTRACT

Question: Does a mailed letter invitation for colonoscopy improve colorectal cancer (CRC) incidence or colorectal cancer associated mortality, compared to those who do not get a mailed invitation?

Study Design: The Nordic-European Initiative on Colorectal Cancer (NordiCC) trial is a pragmatic multi-center randomized controlled trial.

Setting: Poland, Norway, Sweden. Although the Netherlands was part of the original trial, due to Dutch law, the Netherlands investigators were unable to share outcome data on those randomized to the usual care arm.

Participants: Individuals between ages 55-64 who had not had prior CRC screening were eligible and identified from population registries. Those with a history of CRC were excluded. There were 10,374 patients from the Netherlands not included in this report because of inability to share data. Overall, 84,585 participants (64.1% Polish, 31.2% Norwegian, 4.3% Swedish) between 2009-2014 were included in this analysis, 49.9% of all

participants were female and 50.1% were ages 55-59.

Intervention: Study patients were randomized 1:2 to get a personal letter of invitation for screening colonoscopy by mail with an information leaflet about the study vs usual care (i.e., no mailed invitation sent and not informed about their enrollment in the trial at inclusion or during follow-up). Patients in the invitation group also received an informed consent to complete if they chose to participate.

Outcomes: Primary outcomes were risk of CRC and death from CRC with an initial analysis after 10 years and a follow-up analysis after 15 years.[1] The current publication reports results after median 10 years of follow-up. Secondary outcome was all-cause mortality.

Data Analysis: Intention-to-screen analysis where usual care participants were compared to study participants who were mailed an invitation to colonoscopy, regardless of whether or not these individuals underwent colonoscopy. A separate adjusted per-protocol analysis was performed only using study participants who completed a colonoscopy. Kaplan-Meier estimates were calculated to assess the cumulative 10-year risks of CRC and CRC-related deaths.

Results: Of the 28,220 individuals who were sent a mailed invitation, 11,843 (42%) completed a colonoscopy and 259 were diagnosed with CRC over median follow-up of 10.0 years (IQR: 9.9-10.0; maximum follow-up=10.0 years). Of the 56,365 participants in the usual care arm, 622 were diagnosed with CRC over 10-year follow up. In the intention-to-screen analysis of participants who were mailed an invitation to colonoscopy (regardless of whether or not colonoscopy was performed) vs usual care, the risk ratio (RR) for CRC incidence was 0.82 (95% confidence interval [CI], 0.70-0.93) and the RR for CRC-related mortality was 0.90 (95% CI 0.64-1.16). In an adjusted per-protocol analysis that compared invited patients who actually underwent colonoscopy vs usual care, the RR for CRC incidence was 0.69 (95% CI 0.55 to 0.83) and CRC-related mortality was 0.50 (95% CI 0.27 to 0.77). There was no difference in all-cause mortality. Of the 11,843 individuals who had a colonoscopy, there were no perforations and 15 (0.13%) had clinically significant bleeding.

Quality indicators for colonoscopy were also reported: good/very good bowel

preparation (91.2%), cecal intubation (96.8%), and adenoma detection rate (ADR) (30.7%). It's unclear from this report if patients with poor prep or failed cecal intubation had repeat colonoscopy. Although mean ADR of study endoscopists was 30.7%, the mean ADR varied from 14.4% in Sweden to 27.1% in Norway to 35.2% in Poland, and prior reports[1] noted that 29% of study endoscopists had an ADR below the recommended minimum threshold of 25%. No data on performance of colon polyp surveillance colonoscopy is available for the study population.

Funding: Research grants in participating countries. Bowel preparations were provided for free in Norway by Dr. Falk Pharma.

COMMENTARY

Why Is This Important?

Until this study was published, we have relied on prospective cohort studies to understand the effectiveness of colonoscopy, which estimated a 40-69% reduction in CRC incidence and 29-88% reduction in death from CRC.[2] This is the first RCT to evaluate the long-term effectiveness of a population-based screening program in reducing CRC incidence and CRC-related mortality.

Key Study Findings

The screening program rolled out in Poland, Norway and Sweden, consisting of sending a mailed colonoscopy invitation to random individuals in the population, was not effective. Only 42% of those invited actually completed a colonoscopy.

Colonoscopy was also very safe with 0 perforations and a 0.13% risk of serious bleeding.

Caution

This study shows that mailing random people an invitation to complete a colonoscopy does not work. This is important information for countries that have a population-based approach to screening, where these results will likely promote multimodal ways of reaching/educating patients and hopefully promote the multiple screening options available, since a simple snail mailer about colonoscopy did not work. It is important to note that this is not how screening is approached in the United States, where medical professionals serve the key role of educating individuals and helping them make personalized decisions about cancer screening. Thus, the effectiveness of this screening program is not applicable to how we provide care in the US.

It is very encouraging that that the colonoscopy procedures in this study were effective. With that said, the magnitude of benefit was less than prior cohort studies conducted in the US. We know that the protective effect of colonoscopy depends on careful inspection to identify and remove

In the adjusted per-protocol analysis of screening patients who actually had colonoscopy, the procedure was effective; there was a 31% decrease in CRC incidence and a 50% decrease in risk of death from CRC over 10 years of follow up.

precancerous lesions. For every 1% increase in ADR, there is a 3% decrease in CRC incidence and 5% decrease in CRC mortality with continued inverse association as ADR increases up to at least 40%.[3] Approximately 29% of endoscopists in the NordICC trial had an ADR below the recommended minimum threshold of 25% and the highest ADR reported was 40%.[1] It is unclear why ADRs were lower among these endoscopists, but possibilities include that most exams were performed without sedation with over 20% of patients reporting "moderate or severe" pain during the procedure. This may have hastened the examination. Overall, colonoscopy seems to be a different procedure in these countries compared to the US where the average ADR for screening colonoscopies has increased in recent years to 39%[4], which is probably due to factors including use of high-definition white light colonoscopy, a well-publicized effort to educate US endoscopists about ADR, and offering sedation to most patients to facilitate a careful inspection.

Also, more follow up time may be needed to see to the full protective benefit of colonoscopy. A recent study from the Polish investigators who contributed to the NordICC study showed that a high-quality negative screening colonoscopy can be protective of CRC for 17 years.[5] Investigators will report outcomes after 15 years, which was also a planned analysis.[1]

My Practice

This study does not change my practice with regards to CRC screening. I will explain to my patients and colleagues that this study shows that the best screening test is the one that gets done and that colonoscopy is highly safe and highly effective in decreasing risk of CRC and death from CRC. I will continue to offer and perform high-quality colonoscopy as a primary screening test or as a follow up after a positive 2-step test, such as fecal immunochemical test. I will strive for top notch quality, including pristine bowel preparations, adequate sedation to allow for thorough inspection, and optimizing lumen exposure and lesion recognition by incorporating new technologies, such as artificial intelligence, as they emerge.

For Future Research

There are multiple RCTs comparing colonoscopy to fecal immunochemical test that are currently underway currently underway[6] in different health settings, including the CONFIRM trial being conducted at US VA Medical Centers. These studies will undoubtedly provide more comprehensive data about the long-term effects of colonoscopy on CRC incidence and mortality.

With that said, it is important to place

results from any study into context and assess how generalizable those results will be to a particular health setting. Bretthauer and colleagues should be commended for conducting a rigorous RCT with an intention-to-screen analysis that was a better fit for health care in Poland, Norway, Sweden, and the Netherlands. Their data demonstrates that performance of population-based CRC screening based on a mailed invitation for colonoscopy is not effective, largely because the majority of these individuals never got colonoscopy. That is useful information, but it's not generalizable to the US setting despite some sensationalized lay media coverage in the US. Finally, we should also remember that studies which measure long-term outcomes, like CRC incidence and mortality, will be outdated when results are reported because of contemporary advances and innovations in colonoscopy quality.

Conflicts of Interest

Dr. Patel reports no conflicts of interest.

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CRC SCREENING

High Adenoma Detection Rate Decreases Post-Colonoscopy CRC in FIT-Based Screening Program: Quality Matters!

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This summary reviews: Wisse PHA, Erler N, de Boer SY, et al. Adenoma Detection Rate and Risk for Interval Postcolonoscopy Colorectal Cancer in Fecal Immunochemical Test-Based Screening: A Population-Based Cohort Study Ann Intern Med 2022; In Press. http://www.doi.org/10.7326/M22-0301.

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STRUCTURED ABSTRACT

Question: What is the association between physician adenoma detection rates (ADRs) and risk of post-colonoscopy colorectal cancer (PCCRC) across a broad range of ADR values in fecal immunochemical test-positive (FIT+) patients?

Design: Population-based cohort study of the Dutch CRC Screening Program, which started in 2014 and offers single FIT biennially to individuals aged 55-75 years old. With the exception of first 6 months of 2014, FIT+ defined as $\geq$ 47 ug of hemoglobin per gram of feces.

Setting: The Netherlands.

Patients: All FIT+ participants who underwent their first colonoscopy in 2014-16 without a CRC diagnosis within the following 6 months. Among

103,900 FIT+ individuals, complete colonoscopies to cecum with adequate bowel preparation were performed by 311 endoscopists who had performed at least 100 colonoscopies during the study period. Patient demographics: 60.0% male and the median age was 67 (IQR 63-70).

Exposure: ADR of each endoscopist who performed at least 100 colonoscopies and had complete data collection during 2014-2016 was recorded. Endoscopists who perform colonoscopies in Dutch CRC screening program have to be accredited and their procedures are audited annually for the following quality indicators: cecal intubation rate ≥ 95%; adequate bowel preparation (Boston Bowel Preparation Score ≥ 6 in ≥ 90% of procedures); withdrawal time (≥ 6 minutes in ≥ 90% of procedures); polyp resection rate (≥90% of polyps resected without requiring a second scheduled colonoscopy for polyp removal); and, ADR ≥ 30%.

Outcome: The primary outcome was time to interval post-colonoscopy CRC, diagnosed at least 6 months after a complete first colonoscopy and before scheduled surveillance colonoscopy. CRC diagnosed at or after the recommended surveillance interval were defined as "other post-colonoscopy CRC" and were not included in analysis of association between ADR and interval post-colonoscopy CRC. The colonoscopy surveillance intervals used in the Dutch program differ from those used in the US. Their scoring system is detailed and essentially equates to 10-year intervals for 0-1 small adenomas, 5-year intervals for single advanced adenoma or multiple small adenomas, and 3-year intervals for multiple advanced and non-advanced adenomas, including right-sided lesions. Study patients were followed through January 1, 2020 for identification of post-colonoscopy CRC, so maximal follow-up was < 6 years.

Data Analysis: Unadjusted hazard ratio and cox proportional hazards model that included endoscopists' ADR, endoscopy setting, patient age and gender, and diagnostic findings at first colonoscopy.

Results: After 359,589 years of follow-up (median follow-up= 52 months), 209 interval post-colonoscopy CRCs were diagnosed. Median ADR of endoscopists was 67% (range 40%-82%). The unadjusted hazard ratio for the ADR with interval post-colonoscopy CRC was 0.95 per 1% increase in ADR (95% confidence interval: 0.93-0.97; $P < 0.001$) and the multi-variate Cox model also demonstrated a 5% decrease in interval post-colonoscopy CRC for every

1% increase in ADR. There was no association with patient gender, most advanced finding at colonoscopy, or surveillance interval with risk of CRC. With respect to other quality indicators, more than 80% of endoscopists met the cecal intubation target (≥ 95%), more than 90% met the adequate bowel preparation target (≥ 90%) and polyp removal rate target (≥90%), and all endoscopists met the minimal ADR threshold (≥ 30%).

Funding: None

COMMENTARY

Why Is This Important?

"You can't improve what you don't measure" is an old adage attributed to Peter Drucker, who is acclaimed as the father of management and quality improvement. Furthermore, as noted in the editorial accompanying this study[1], "if you measure it, it gets done." Therefore, we better make sure that an endpoint is impactful before we put in the time and effort to measure it. In average-risk CRC screening colonoscopy and colonoscopy in FIT+ patients, ADR is clearly worth measuring since our goal is to prevent CRC. Since FIT+ patients are at higher risk for adenomas, these data are very helpful for establishing minimum thresholds and aspirational targets for ADR.

Before a more general discussion about the importance of continuous quality improvement with ADR, a brief note about FIT-based CRC screening may be helpful. In the Dutch program, the FIT+ cutoff of 47 ug per gram of feces is higher than the conventional cut-off of 20 ug per gram of feces used in the US and Asia, which would probably be associated with a lower ADR. In fact, a multi-center Asian randomized controlled trial (RCT)[2] compared ADR in average-risk screening colonoscopy vs FIT+ individuals (20 ug hemoglobin cut-off) and reported mean ADRs of 37.5% vs 53.6% in the 2 groups. Those data may be more helpful to identify a new minimum threshold and aspirational target for ADR in FIT+ individuals.

The current minimum ADR threshold in average-risk CRC screening colonoscopy is 25%[3], although recent data summarized in this publication demonstrates that each 1% increase in ADR is associated with a 3% decrease in interval post-colonoscopy CRC up to ADRs of 40%[4]. Simply achieving an ADR of 25% is a bare minimum. Yet, in a summary[5] by Swati Patel, MD, MS, 29% of the study endoscopists in the NordiCC RCT failed to achieve this minimum threshold, which may account for a smaller reduction in CRC incidence with colonoscopy than would be estimated based on available prospective cohort studies.

Ultimately, ADR is an ideal quality improvement measure. Research demonstrates that it's associated with the outcome of interest (reduction in CRC), is

easily measured, varies widely with ADRs ranging from 8% to 62% in the control arms of different colonoscopy RCTs[6], and can be improved through multiple interventions, including simply measuring and reporting ADRs back to endoscopists as well as improving quality of bowel preparation, increasing withdrawal time, using distal colonoscopy attachments, and employing artificial intelligence systems to help identify polyps. Wisse and colleagues are to be commended for producing an outstanding study to confirm the importance of raising ADRs in the FIT+ screening population that undergo colonoscopy.

Caution

Sessile serrated lesions were not included in the ADR calculation, which is consistent with the current standard ADR definition. Since study patients had their initial colonoscopy in 2014-2016, median follow-up of patients was 52 months. Longer follow-up would be helpful for patients scheduled for repeat colonoscopy 10 years after initial colonoscopy. As noted above, the cut-off for FIT+ was 47ug per gram of feces, which may have contributed to the very high median ADR seen in this study.

My Practice

In our Veterans Affairs Medical Centers, the default CRC-screening tool is FIT with a positive test defined as $\geq$ 20ug hemoglobin per gram of feces. Screening colonoscopy is available if patient requests it after discussion with their primary care provider. At the John D. Dingell VAMC, we report separate ADRs for colon polyp surveillance colonoscopy, FIT+ screening colonoscopy, and average-risk screening colonoscopy, along with cecal intubation rate, withdrawal time for colonoscopies when no polyps are removed, and frequency of adequate bowel preparation in biannual reports. In order to improve ADRs, our endoscopists are routinely taught to take a second look in the right side of the colon and have the option of using Endocuff (Olympus America), a distal cap device used to distend folds. Fortunately, we have high-definition white light colonoscopy systems and we're scheduled to install GiGenius (Medtronic), an artificial intelligence system to improve identification of polyps in real-time during colonoscopy.

Key Study Findings

In this population of FIT+ individuals undergoing CRC screening colonoscopy, each 1% increase in ADR was associated with a 5% decrease in interval post-colonoscopy CRC across endoscopists with median ADR 67% (range 40-82%).

For Future Research

Future guidelines and position statements should be updated to reflect higher threshold ADRs when screening colonoscopy is performed in FIT+ patients. Prior summaries in this publication have outlined multiple interventions for improving ADR. Given the robust data about the impact of ADR on quality of screening colonoscopy, future research may shift focus to quantifying the number of US endoscopists/endoscopy units that routinely calculate

and report ADRs and explore implementation of quality improvement programs in units that aren't measuring it.

Conflicts of Interest

Drs. Sleiman and Schoenfeld declare no conflicts of interest.

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EVIDENCE-BASED GI
AN ACG PUBLICATION

Acute Pancreatitis: Need IV Fluid Resuscitation But Avoid a WATERFALL!

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This summary reviews: de-Madaria E, Buxbaum JL, Maisonneuve P, et al. Aggressive or Moderate Fluid Resuscitation in Acute Pancreatitis. N Engl J Med 2022;387(11):989-1000. http://www.doi.org/10.1056/NEJMoa2202884.

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STRUCTURED ABSTRACT

Question: What degree of intravenous (IV) fluid hydration leads to optimal outcomes in acute pancreatitis?

Design: Multi-center, prospective randomized control trial (RCT), entitled the WATERFALL study (the Early Weight-Based Aggressive vs Nonaggressive Goal-Directed Fluid Resuscitation in the Early Phase of Acute Pancreatitis).

Setting: Eighteen centers across 4 countries: India, Italy, Mexico, and Spain.

Patients: Adults at least 18 years of age who met clinical criteria of acute pancreatitis (Revised Atlanta Classification: meeting 2 of the following 3: classical abdominal pain, serum amylase or lipase level higher than 3 times the upper limit of the normal, or signs of acute pancreatitis on imaging) were screened for enrollment. The trial only included patients

who received a diagnosis of acute pancreatitis within 8 hours prior to screening and had presented to the emergency room within 24 hours of pain onset. Those with severe disease at baseline, including respiratory, heart, or kidney failure, chronic pancreatitis, or other severe comorbidities including uncontrolled arterial hypertension, hypernatremia, hyponatremia, hyperkalemia, hypercalcemia, decompensated cirrhosis, or low life expectancy were excluded. Patients provided informed consent to participate in the trial.

Interventions: Patients were randomly assigned (in a 1:1 ratio) to receive aggressive fluid resuscitation or moderate fluid resuscitation with lactated Ringer's solution. The groups are depicted in **Table 1**. In both groups, investigators performed an initial physical assessment at 0 hours to evaluate for fluid overload, and additional assessments at 3, 12, 24, 48, and 72 hours. As such, hydration was decreased or stopped if there was suspicion of fluid overload in both groups. Oral feeding was started at 12 hours if there was a lower degree of abdominal pain. Fluid resuscitation was stopped once a patient was tolerating oral feeding for 4 hours.

Outcomes: Primary outcome was the development of moderately severe or severe acute pancreatitis during hospitalization, defined as meeting at least 1 of the following criteria: local complications, exacerbation of a pre-existing coexisting condition, a creatinine level of at least 1.9 mg per deciliter (170 μmol per liter), a systolic blood pressure of less than 90 mm Hg despite fluid resuscitation, and a ratio of the partial pressure of arterial oxygen (Pao2) to the fraction of inspired oxygen (Fio2) of no more than 300. Multiple secondary outcomes were assessed, including organ failure, intensive care unit admission, infected necrotizing pancreatitis, persistent symptoms, and need for nutritional support, among others. The main safety outcome was fluid overload and required meeting at least 2 of the following 3 criteria: symptoms, physical signs, and imaging evidence of hypervolemia.

Data Analysis: The primary outcome, development of moderately severe or severe acute pancreatitis, was evaluated for superiority with an intention-to-treat analysis. There were 3 *a priori* stopping rules: (1) a between-group difference in the primary outcome with a 2-sided *P* value of less than 0.0002 at interim analysis or of less than 0.012 at the second interim analysis; (2) clear evidence of harm in 1 trial group over the other (safety) by the data and safety monitoring board; and (3) a slow recruitment rate.

Results: Two hundred forty-nine patients were randomized: 122 patients to the aggressive resuscitation group and 117 patients to the moderate resuscitation group. There were no significant differences between the groups regarding age, sex, gallstones as ideology of the pancreatitis, body mass index, comorbidities and severity, baseline abdominal pain severity, pancreatitis severity, lab markers, respiratory status, or hypovolemic status.
There was no significant difference in the development of the primary outcome, moderately severe or severe acute pancreatitis, which occurred in 22.1% of the aggressive resuscitation group and 17.3% of those in a moderate resuscitation group. Most importantly, aggressive fluid resuscitation was associated with a significantly higher incidence of fluid overload: 20.5% vs 6.3% (adjusted relative risk, 2.85; 95% confidence interval [CI], 1.36 to 5.94). Accordingly, the data and safety monitoring board halted the trial owing to significantly worse results with respect to safety outcomes, and the lack of trend toward improved outcomes. The notable findings are summarized in **Table 2.** Given that the trial was halted, subgroup analyses were limited but fluid overload was also noted in the subgroups of patients with or without systemic inflammatory response syndrome and those with hypovolemia.

Funding: Grants from the Instituto de Salud Carlos III, the Spanish Association of Gastroenterology, ISABIAL (Instituto de Investigación Sanitaria y Biomédica de Alicante), the Italian Ministry of Health, Ricerca Corrente, and 5x1000.

Table 1: Fluid Resuscitation Strategies

	Aggressive fluid resuscitation	Moderate fluid resuscitation
At 0 hours	Bolus 20 ml/kg, then infusion 3 ml/kg/hr	Infusion 1.5 ml/kg/hr, preceded by bolus 10 ml/kg only if patient has hypovolemia
At 3 hours Safety Checkpoint	If there is suspicion of fluid overload, decrease or stop infusion	
At 12, 24, 48, and 72 hrs Goal-Directed Therapy Checkpoints	❖ Hypovolemia - Bolus 20 ml/kg, then infusion 3 ml/kg/hr - Additional boluses of 20 ml/kg if urine output <0.5 ml/kg/hr or SBP <90 mm Hg ❖ Normovolemia - Infusion 1.5 ml/kg/hr - Infusion stopped after 48 hr if oral feeding tolerated for >8 hr ❖ Suspicion of fluid overload - Decrease or stop infusion - Infusion stopped after 48 hr if oral feeding tolerated for >8 hr	❖ Hypovolemia - Bolus 10 ml/kg, then infusion 1.5 ml/kg/hr - Additional boluses of 10 ml/kg could be administered in case of urine output <0.5 ml/kg/hr or SBP <90 mm Hg ❖ Normovolemia - Infusion 1.5 ml/kg/hr - Infusion stopped after 20 hr if oral feeding tolerated for >8 hr ❖ Suspicion of fluid overload: - Decrease or stop infusion - Infusion stopped after 20 hr if oral feeding tolerated for >8 hr

Table 2: Outcomes in Each Group		
	Aggressive fluid resuscitation	**Moderate fluid resuscitation**
Moderately severe or severe pancreatitis	22.1%	17.3%
Fluid overload	20.5%	6.3%
Total fluid volume administered	7.8 liters (interquartile range, 6.5 to 9.8)	5.5 liters (interquartile range, 4.0 to 6.8)
Organ failure	7.4%	3.9%
Persistent organ failure	6.6%	1.6%
Respiratory failure	7.4%	2.4%
Necrotizing pancreatitis in 13.9%	13.9%	7.1%
ICU need	6.6%	1.6%
Median duration of hospitalization	6 days (IQR 4-8)	5 days (IQR 3-7)

COMMENTARY

Why Is This Important?

Acute pancreatitis is a vexing problem – there is no clear pharmacologic therapy that has been shown to be of benefit. A standard guideline-recommended intervention is "early aggressive hydration" during the first 12–24 hours.[1] However, the basis of this is theoretical, and the goal is to avoid the intravascular depletion that occurs in pancreatitis, secondary to vomiting, reduced oral intake, third-spacing of fluids, increased respiratory losses, and diaphoresis, with researchers hypothesizing that the third-spacing contributes to pancreatic necrosis and death.[2,3] In fact, studies are conflicting regarding early aggressive hydration in acute pancreatitis, with some showing benefit[4-6] while others show harm.[7,8] Furthermore, not only is it unclear if it is beneficial, but the term "early aggressive hydration" is vague – there is limited clear guidance about how much fluid, when to start, or when to stop. The WATERFALL study is a well-designed and clinically relevant randomized control trial that overcomes methodological issues of prior studies.

Key Study Findings

This well-designed RCT compares moderate and aggressive fluid resuscitation strategies in acute pancreatitis.

There was no significant difference in the incidence of moderately severe or severe pancreatitis between groups (22.1% in the aggressive-resuscitation group and 17.3% in the moderate-resuscitation group; adjusted relative risk, 1.30; 95% CI, 0.78 to 2.18; *P*=0.32), but there were significantly higher rates of fluid overload in the aggressive fluid resuscitation arm: 20.5%, compared to the moderate fluid resuscitation arm: 6.3% (adjusted relative risk, 2.85; 95% CI, 1.36 to 5.94, *P*=0.004).

Therefore, per *a priori* stopping rules,

the trial was halted by the data safety and monitoring board.

Caution

Given the nature of this RCT, there are some methodologic limitations that could not be overcome. First, it is underpowered due to being halted by the data and safety monitoring board. As such, outcomes were unable to be assessed in a statistically sound manner. It was unblinded, which would have been impractical. Lastly, patients in this trial tended to be younger than most acute pancreatitis patients, likely due to the exclusion of patients with heart or kidney failure. Nevertheless, this heightens our caution to avoid overly aggressive fluid resuscitation in patients with acute pancreatitis.

My Practice

This study has made us more cautious about fluid management in acute pancreatitis. Previously, we would monitor volume status. Now, we are even more vigilant, given the clear harm that aggressive fluid resuscitation can entail. Currently, we follow the authors' strategy: an initial fluid rate of 1.5 mL/kg of body weight/hour with boluses only for signs of hypovolemia. We frequently and carefully reassess to avoid volume overload in the first 72 hours with consideration given to diuresis as needed.

A point of interest for us is how this study developed. The first-author, Dr. Enrique de-Madaria, has commented on how a clinical question inspired this paradigm-shifting WATERFALL study – and we are inspired by how a clinical observation regarding a gap in the literature led to such a monumental effort and this multi-center international trial with striking results (https://twitter.com/demadaria/status/1570165278587207680?s=42&t=Wpl242NtG5NaC-1i618fsA).

For Future Research

Since routine aggressive fluid resuscitation can be harmful, we need to identify what moderate resuscitation strategy improves outcomes. This trial only tested 1 moderate-resuscitation strategy. We also need to optimize outcomes for those patients who were excluded from this trial, including those with respiratory, kidney or heart failure at baseline. Lastly, we need pharmacologic therapy: a 17.3% incidence of moderately severe or severe pancreatitis in the moderate-resuscitation group–the arm with "better" outcomes–speaks to how much room for improvement there is.

Conflicts of Interest

Dr. Kumar and Dr. Gardner report no conflicts of interest.

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

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