Welcome to the first issue of Evidence-Based GI: An ACG Publication. Our goal is straightforward: to provide structured abstracts and expert commentary on the best clinical GI, hepatology, and endoscopy research published in the leading general medicine journals as well as European GI journals. We hope to further the educational mission of the American College of Gastroenterology (ACG) and help members to deliver compassionate, evidence-based GI patient care of the highest quality.

Even though I diligently review The American Journal of Gastroenterology, Gastroenterology, Gastrointestinal Endoscopy, and Clinical Gastroenterology and Hepatology each month, my GI fellows regularly find a way to humble me. It is a little embarrassing to teach that a family history of gastric cancer is an indication to test for Helicobacter pylori, only to have a GI fellow teach me about a recent randomized controlled trial in The New England Journal of Medicine which found that H. pylori treatment significantly reduced the incidence of gastric cancer in those patients.¹ Just another reminder that it’s very difficult to stay current with published GI research.

In Evidence-Based GI, we’ll update you about outstanding clinical GI research published in general medicine journals, such as The New England Journal of Medicine, Annals of Internal Medicine, and JAMA, as well as vital work published in the journals of European GI Societies, specifically GUT, Endoscopy, and the Journal of Hepatology. As an ACG publication, we will also
summarize a key study from our flagship Red Journal in each issue. However, our aim is to educate ACG members about the best GI clinical research studies coming from journals that they may not see each month.

Each of our Associate Editors have advanced degrees in clinical epidemiology or public health, and we are advocates of evidence-based medicine (EBM). We will apply EBM methodology to identify well-designed studies which minimize bias in order to produce accurate results. Then, we will explain study results in easy-to-use terms to facilitate the application to patient care. It is important to remember that “EBM” could also be used to describe “experience-based medicine,” and that no single study provides definitive data about how to treat each unique patient. For this reason, each commentary will include a “My Practice” section where the author will discuss how they combine the research data and their own experience when treating individual patients.

I am indebted to several mentors for inspiring this work. R. Brian Haynes, MD, PhD, is Professor (Emeritus) and Past Chair of the Department of Clinical Epidemiology at McMaster University in Hamilton, Ontario, and the inaugural Editor of the *ACP Journal Club* publication—now a subsection of *Annals of Internal Medicine*. He invited me to write commentaries for that journal after an EBM seminar in the 1990s which started my academic career. In some ways, this publication is an homage to *ACP Journal Club*, which I see as the gold standard for producing evidence-based summaries of clinical research. Also, Gordon Guyatt, MD, MSc, who coined the phrase “Evidence-Based Medicine,” and Deborah Cook, MD, MSc, are true pioneers of EBM who spent countless hours teaching me EBM concepts. As this publication evolves, I will do my best to apply their lessons and teachings. Finally, Douglas Rex, MD, MACG, and past president of the ACG roused me from my COVID lockdown-induced stupor when he started *ASGE JournalScan*, which reviews endoscopic research. It is a terrific tool for endoscopists to identify studies that they may have
missed. Although Evidence-Based GI has different aims and objectives, I would be remiss if I did not acknowledge how Dr. Rex’s work inspired me to work on this project. Finally, thanks to Deepak Parakkal, MD, FACG, Chair of the ACG Digital Communications and Publications Committee, and the current ACG President, David Greenwald, MD, FACG, for supporting this project as well as Anne-Louise Oliphant, ACG Vice President of Communications, Claire Neumann, ACG Managing Editor, Kavitha Gnanasekhar, ACG Assistant Managing Editor and Kate Langenberg, ACG Editorial Coordinator for making this project work.

This is a work in progress, and although the format, content, and presentation of the publication may change over time, our mission will remain the same. We are trying different approaches, including audio summaries that accompany each article. Each summary should be easily read in 5 minutes on one’s electronic device, and we are experimenting with graphical displays of key study findings. A glossary with definitions of different methodological and statistical terms will be added along with links to EBM guides for evaluating the medical literature. I welcome comments, and thank you for joining us on this journey.

Reference

Semaglutide Produces Mean Weight Loss of 34 Pounds over 68 Weeks in Obese and Overweight Individuals-A Huge “STEP” in Medical Management of Obesity

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STRUCTURED ABSTRACT

Question: Is high-dose semaglutide (Wegovy®), a GLP-1 analogue used for Type II diabetes mellitus (DM), effective and safe for sustained weight loss when used with lifestyle interventions.

Design: Randomized, double-blind, placebo-controlled trial. Randomized in 2:1 ratio for semaglutide vs placebo.

Setting: One hundred twenty nine sites in 16 countries in South and North America, Asia, and Europe

Patients: There were 1961 adults with either BMI ≥ 30 or BMI ≥ 27 plus ≥ 1 weight-related condition (e.g., hypertension, obstructive sleep apnea, cardiovascular disease, etc.) with approximately 75% White, 74% women, 44% prediabetics and mean body weight of 230 pounds. Exclusion criteria included diabetes, history of acute pancreatitis in past 6 months, chronic pancreatitis, and previous obesity surgery.

Exposure/Intervention: Weekly subq semaglutide vs placebo injected in pre-filled pen injector plus lifestyle intervention defined as individual counseling
sessions to improve adherence to reduced-calorie diet and increased physical activity. Initial semaglutide dose was 0.25mg per week and was increased every 4 weeks to reach goal dose of 2.4mg per week by week 16.** Outcome:** Co-primary endpoints of mean percentage reduction in body weight and proportion of individuals with ≥ 5% reduction in body weight from baseline at week 68.** Data Analysis:** Intention-to-treat and per-protocol analysis reported.** Funding:** Novo Nordisk, manufacturer of semaglutide, designed and executed the study as well as funding the study.** Results:** Mean reduction in body weight was 14.9% with semaglutide plus lifestyle intervention vs 2.4% with placebo plus lifestyle intervention. At 68 weeks, mean total reduction in weight was greater with semaglutide vs placebo: 33.7 pounds vs 5.7 pounds (Figure 1). Significantly more patients in semaglutide group achieved at least 5% reduction in body weight (86.4% vs 31.5%), 10% reduction in body weight (69.1% vs 12.0%), or 15% reduction in body weight (50.5% vs 4.9%). Nausea (44.2% vs 17.4%) and diarrhea (31.5% vs 15.9%) were more common in the semaglutide group vs placebo and discontinuation of medication due to GI side effects was also higher in semaglutide group (4.5% vs 0.8%).

Why is this important? Obesity is a global health epidemic, and the only treatment associated with long-term and sustained weight loss is bariatric surgery or endoscopic sleeve gastrectomy, which usually produce about 20% reduction in body weight. These data indicate that semaglutide (Wegovy®) is far superior to currently available weight loss medications. For example, naltrexone/bupropion (Contrave®) produces about 5% body weight reduction and phentermine/topiramate (Qysmia®) is associated with about 8% reduction. This is a true breakthrough. Although endocrinologists and other providers certified in obesity medicine are providing much of obesity management right now, gastroenterologists are frequently asked about weight loss, becoming certified in obesity medicine, and performance of bariatric endoscopy is advancing.
Key study findings: Mean reduction in body weight of almost 15%, which equates to mean loss of almost 34 pounds, was found in the semaglutide group and maintained over 68 weeks. This is far superior to weight loss observed with any other medication. Approximately 1/3 of semaglutide patients achieved 20% body weight reduction, which is similar to weight reduction with bariatric surgery or endoscopic sleeve gastrectomy. Caution: GI adverse events, specifically nausea (44.2%) and diarrhea (31.5%), clearly occur frequently, although only about 5% of semaglutide-treated patients discontinued medication due to these GI adverse events. In our practice, patients usually develop clinically important nausea or diarrhea within the first few weeks of use and these symptoms resolve with discontinuation of medicine. Rapid weight loss is associated with developing cholelithiasis, which occurred in about 2% of semaglutide-treated patients. Insurance often becomes an issue for semaglutide (Wegovy®) coverage, especially in Medicaid and Medicare Part D coverage. Remember—the treatment should be combined with counseling from a dietitian on reduced calorie diets and increased physical activity. Insurance coverage for dietitians is variable unless the patient also has diabetes.
**My practice:** In Dr. Paul’s hepatology practice, which includes many NASH patients, most obese and overweight patients with one additional risk factor are prescribed semaglutide. Currently, this practice has become so popular shortages are occurring at some pharmacies. We educate patients that mild nausea/diarrhea may occur as dose is escalated and that medication can be discontinued if symptoms become severe. All of our patients must also see a dietitian for counseling.

**For future research:** Better data across all racial/ethnic groups, in men, and in obese diabetic patients will be helpful. For gastroenterologists, more data about combination therapy with bariatric endoscopy from well-designed, prospective studies will be crucial for optimal management of obesity. With the rapidly rising prevalence of non-alcoholic steatohepatitis (NASH), semaglutide (Wegovy®) may be particularly helpful in this GI population, and a future summary will review a separate placebo-controlled, double-blind RCT that assessed efficacy of semaglutide to reduce fibrosis scores in NASH patients.

**References**


Piecemeal Cold Snare Polypectomy of Large Sessile Serrated Polyps Is Safe and Effective: Cold is the New Hot!

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STRUCTURE ABSTRACT

Question: Is piecemeal cold snare polypectomy of sessile serrated lesions (SSL) ≥ 20 mm safe and effective compared to hot snare endoscopic mucosal resection?


Setting: Four tertiary referral centers in Australia. Data from the Australian Colonic Endoscopic Resection study where patient, procedural, short- and long-term follow up data were prospectively collected.

Patients & Lesions: Lesions ≥ 2 cm with Kudo II (O) pit pattern (i.e., consistent with serrated polyp histology) were included (Figure 1). Lesions with features consistent with adenomas/dysplasia (Kudo III or IV pit pattern) or submucosal invasion (Kudo V pit pattern) were excluded from the cold snare group. 156 SSLs (median size 25 mm) treated by piecemeal cold snare polypectomy between 2016-2020 from 121 patients (median age 60 and 70.2% female) were compared to 406 SSLs (median size 25 mm) removed by standard hot snare endoscopic mucosal resection from 2008-2016 from 353 patients (median age 66 and 65.2% female).
**Intervention:** All lesions were examined under high-definition white light and narrow band imaging. Lesions were lifted with succinylated gelatin, 0.4% indigo carmine and 1:100,000 epinephrine. A dedicated cold snare was used to remove the lesion piecemeal ensuring a wide rim (≥3 mm) of normal mucosa at peripheral margins. Conventional hot snare endoscopic mucosal resection was performed per usual technique and snare-tip soft coagulation of the resection margin.

**Funding:** Westmead Medical Research Foundation, University of British Columbia Clinician Investigator Fellowship, Gallipoli Medical Research

**Results:** Piecemeal cold snare had 100% technical success per lesion, with no adverse events per patient (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Summary of findings</th>
<th>Piecemeal cold snare</th>
<th>EMR hot snare</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical success per lesion</td>
<td>100%</td>
<td>99.0%</td>
<td>1</td>
</tr>
<tr>
<td>Adverse Events per patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically significant intra-procedural bleeding</td>
<td>0%</td>
<td>1.4%</td>
<td>0.336</td>
</tr>
<tr>
<td>Deep Mural Injury</td>
<td>0%</td>
<td>2.8%</td>
<td>0.071</td>
</tr>
<tr>
<td>Clinically significant post-EMR bleeding</td>
<td>0%</td>
<td>5.1%</td>
<td>0.010</td>
</tr>
<tr>
<td>Delayed perforation</td>
<td>0%</td>
<td>0.6%</td>
<td>1</td>
</tr>
<tr>
<td>Recurrence per patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>4.3%</td>
<td>4.6%</td>
<td>0.931</td>
</tr>
<tr>
<td>18 months</td>
<td>2.0%</td>
<td>1.2%</td>
<td>0.523</td>
</tr>
</tbody>
</table>

**Figure 1.** Large sessile serrated lesion without features of dysplasia or submucosal invasion under high-definition white light (A) and narrow band imaging (B).
Why is this important? Up to 30% of all colorectal cancers (CRCs) arise from sessile serrated lesions (SSLs) through the serrated colorectal neoplasia pathway. These lesions are usually located in the proximal colon, are flat, have an overlying mucous cap and have indistinct borders. Because of these endoscopic characteristics, these lesions are frequently missed, prone to incomplete resection and therefore disproportionately represent the precursor lesions to post-colonoscopy cancers. Thus, in addition to careful inspection during colonoscopy to minimize missed lesions, it is critically important to ensure complete endoscopic resection of SSLs.

The standard of care for removal of these lesions has been to perform endoscopic mucosal resection (EMR) with a hot snare and more recently to treat the resection margins with snare tip soft coagulation. EMR is associated with a risk of delayed post-polypectomy bleeding and deep mural injury, defined according to the Sydney classification as grade III (muscularis propria injury or ‘target sign’) or grade IV/V (transmural perforation without or with contamination, respectively). Given that SSLs have less submucosal fibrosis than adenomas, van Hattem et al. hypothesized that removing SSLs without submucosal invasion via piecemeal cold snare polypectomy may be just as effective as EMR. Furthermore, without electrocautery, the authors posited that the risks of delayed post-polypectomy bleeding and deep mural injury would be lower.

Key study finding: Piecemeal cold snare polypectomy had 100% technical success, similar recurrence rates (< 5% at 6 and 18 months), and 0% adverse event rate with significantly lower rate of post-EMR bleeding compared to conventional EMR, and the authors concluded that this technique should be considered standard of care for these lesions.

Caution: Lesions were only removed by piecemeal cold snare polypectomy if they were SSLs and had no evidence of adenomas/dysplasia based on optical diagnosis. Furthermore, all lesions were lifted with a dye agent and epinephrine and removed using a dedicated cold snare (i.e., snare designed specifically for cold snare polypectomy). Although all lesions in this study were resected by an experienced endoscopist, widespread use of cold snare suggests that any endoscopist can adopt this approach for large serrated lesions.

My practice: I dedicate time and effort to adequately cleansing the lesion (to wash off any mucous cap) and thoroughly inspect the lesion under high-definition white light and Narrow Band Imaging (NBI) to ensure the lesion is an SSL based on Workgroup on Serrated polypS and Polyposis (WASP) criteria and does not have any features of adenomas/dysplasia (Kudo III or IV pit pattern) or submucosal invasion (Kudo V pit.
pattern). I lift all lesions with a dye-based colloid injectate. Specifically, I use ORISE (Boston Scientific, Marlborough, MA), but Elevie (Aries Pharmaceuticals, San Diego, CA) is appropriate, too. I also use a snare designed specifically for more complex cold snare polypectomy instead of a standard oval snare. Currently, I’m using the Captivator™ COLD Single-Use Snare (Boston Scientific, Marlborough, MA), but the Exacto Cold Snare (Steris, Mentor, OH) is good, too. I work to ensure no mucosal islands and a wide resection margin of at least 3mm along the periphery of the lesion. I do not routinely use epinephrine in my injection solution because I have not found the mild oozing at the resection base to interfere with visualization nor cause sustained bleeding requiring intervention.

For future research: More data is needed to determine if an injection solution is required and whether piecemeal cold snare polypectomy is a suitable for SSLs with features of dysplasia, which could be particularly important for serrated polyposis syndrome patients with numerous lesions.

References

Screening Colonoscopy Decreases Colorectal Cancer Incidence and Colorectal Cancer-related Mortality in Patients > 75 Years Old… As long as They Are HEALTHY!

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STRUCTURED ABSTRACT

Question: Does screening endoscopy (colonoscopy or sigmoidoscopy) reduce colorectal cancer (CRC) incidence and CRC-related mortality in individuals > 75 years old with or without significant comorbidities?

Design: Prospective cohort study of male clinicians (Health Professionals Follow-Up Study) and female nurses (Nurses’ Health Study) from 1988-2016.

Setting: The Nurses’ Health Study was established in 1976 with 121,701 married registered nurses, aged 30-55, in the 11 most populous US states and the Health Professionals Follow-Up Study was established in 1986 with 51,529 male “clinicians” (e.g., physicians, optometrists, podiatrists, etc.), aged 40-75. Both groups completed bi-annual questionnaires about demographics, lifestyle factors, medical history and disease outcomes.

Patients: There were 56,374 participants who reached age 75 during follow-up between 1988-2016 with 63.2% women and 36.8% men.

Exposure/Intervention: History of screening sigmoidoscopy or colonoscopy (average risk or positive family history of CRC) prior to or at age 75 and after age 75.
**Outcome:** Incidence of CRC and CRC-related mortality based on reporting in health questionnaires and confirmed by review of pathology reports, medical records, and National Death Index.

**Data Analysis:** Hazard ratios determined by Cox proportional hazards regression models with sub-group analysis based on presence of co-morbidities, including cardiovascular disease (myocardial infarction or stroke), hypertension, diabetes, and hypercholesterolemia.

**Results:** Compared to no screening, screening endoscopy (i.e., colonoscopy or sigmoidoscopy) after 75 years of age was associated with a 39% reduced risk for CRC incidence (adjusted hazard ratio (aHR): 0.61; 95% confidence interval (CI): 0.52-0.74) and a 40% reduced risk for CRC-related mortality (aHR: 0.60; 95%: 0.46-0.78), regardless of any prior screening history (Table). The study also found no benefit in CRC-related mortality among individuals who underwent screening endoscopy after age 75 years if they had either cardiovascular disease defined as history of myocardial infarction or stroke (aHR: 1.18; 95% CI, 0.59-2.35) or at least three significant co-morbidities defined by hypertension, diabetes, hypercholesterolemia, and cardiovascular disease (aHR: 1.17; 95% CI, 0.57-2.43), although interactions were not statistically significant.

**Table. Summary of findings**

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Adjusted Hazard Ratio for CRC Incidence</th>
<th>Adjusted Hazard Ratio for CRC-related mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening endoscopy after age 75 years (regardless of any prior screening history)</td>
<td>0.61 (0.46-0.78)</td>
<td>0.60 (0.46-0.78)</td>
</tr>
<tr>
<td>Screening endoscopy after age 75 years (with prior screening before age 75 years)</td>
<td>0.67 (0.50-0.89)</td>
<td>0.58 (0.38-0.87)</td>
</tr>
<tr>
<td>First screening endoscopy after age 75 years</td>
<td>0.51 (0.37-0.70)</td>
<td>0.63 (0.43-0.93)</td>
</tr>
</tbody>
</table>

**Why is this important?** At what age should CRC screening be discontinued? Recent guidelines from the United States Preventive Services Task Force (USPSTF) and the American College of Gastroenterology (ACG) recommend CRC screening should continue until age 75 years, followed by individualized screening decisions for adults 76-85 years of age.¹² The latter recommendation is largely based on modeling studies because most trials have excluded individuals > 75 years old. This is the first well-designed
prospective observational cohort study to assess the impact of screening in individuals >75 years old on CRC incidence and CRC-related mortality.

**Key study findings:** CRC screening with endoscopy significantly reduces both CRC incidence and CRC-related mortality in individuals > 75 years old, regardless of prior screening history (Figure 1). However, this benefit appears to be seen among individuals who DO NOT have a history of cardiovascular disease (i.e., myocardial infarctions or stroke) or three or more significant co-morbidities (e.g., hypertension, diabetes, hypercholesterolemia, and cardiovascular disease).

![Figure 1.](image)

**Caution:** Although the Nurses’ Health Study and the Health Professionals Follow-Up Study are the gold standard for prospective cohort studies in the United States in terms of methodology, the study participants are mostly White health care professionals, which limits generalizability. Also, confounding by indication is possible. Specifically, the improved CRC incidence and CRC-related mortality could be due to self-selection of “healthier” patients to be screened as opposed to actual benefit of screening. The authors acknowledged that the number of incident cases was too small to allow sub-group analysis in patients with other co-morbidities like congestive heart failure or chronic kidney disease.
My practice: For patients > 75 years old, I provide an individualized recommendation based on their age, co-morbidities, life-expectancy (e.g., ePrognosis – http://eprognosis.ucsf.edu), preferences and values, and prior screening history. Although using a tool like ePrognosis takes a few moments to use, it can be very helpful to quantify likely life expectancy. It’s probably worth the effort when you are uncertain about the appropriate recommendation.

I usually advise screening if the individual has no significant co-morbidities and likely life expectancy of 5-10 years, but I generally advise against screening if they have cardiovascular disease or multiple co-morbidities, like diabetes, hypertension, hypercholesterolemia or even others such as chronic lung disease, congestive heart failure or significant smoking history.

For future research: More data is needed to assess benefit of screening across all racial/ethnic groups, in 80–84 year-olds vs 75-79 year-olds, and to identify other co-morbidities that mitigate the benefit of screening.

References


Thiopurine use in IBD patients associated with one additional case of acute myeloid leukemia/myelodysplastic syndrome per about 7500 patient-years of use

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Original Citation: Khan N, Patel D, Trivedi C, et al. Incidence of Acute Myeloid Leukemia and Myelodysplastic Syndrome in Patients with Inflammatory Bowel Disease and the Impact of Thiopurines on Their Risk. Am J Gastroenterol 2021; 116: 741-47. https://doi.org/10.14309/ajg.0000000000001058
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STRUCTURED ABSTRACT

Question: Do thiopurines (azathioprine, 6-mercaptopurine, and thioguanine) increase the risk of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) in inflammatory bowel disease (IBD) patients?

Design: Retrospective cohort study using nationwide electronic medical record data

Setting: US Veterans Affairs Healthcare System

Patients: 56,314 Veterans with Crohn’s disease or ulcerative colitis diagnosed between 2000-18 based on ICD-9/ICD-10 codes

Exposure/Intervention: (a) never exposed to thiopurines; (b) past use of thiopurines; (c) current use of thiopurines < 2 years; or (d) current use of thiopurines ≥ 2 years

Outcome: AML or MDS initially identified by ICD codes and/or CPT codes followed by review of individual patient records.

Data Analysis: Multivariable Cox proportional hazards regression model in order to reduce confounding of the results by age, sex, race, IBD subtype, other IBD medications, medical comorbidities, and environmental/military toxic exposures
Funding: Pfizer pharmaceutical company provided an unrestricted research grant. Pfizer had no role in any portion of study.

Results: Among 56,314 veterans with IBD, 107 subsequently developed AML/MDS. Compared to no exposure to thiopurines, current thiopurine use was associated with 2-3X higher adjusted rates of AML/MDS. Adjusted HR = 3.05 (95% CI: 1.54-6.06) for < 2 years of use and adjusted HR = 2.32 (95% CI: 1.22-4.41) for > 2 years of exposure. Overall, risk is still quite low with AML/MDS rate of 17.0 per 100,000 person-years of follow-up in IBD patients at baseline and 1 additional case of AML/MDS for approximately 7500 person-years of thiopurine exposure (Table 1).

Table 1. AML/MDS Diagnoses

<table>
<thead>
<tr>
<th>Thiopurine exposure</th>
<th>Rate per 100,000 person-years (95% CI)*</th>
<th>Adjusted hazard ratio</th>
<th>Person-years of thiopurine use to cause one additional AML/MDS diagnosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>17.0 (16.9 - 17.1)</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>Current, &lt;2 years cumulative use</td>
<td>30.4 (29.8 - 31.0)</td>
<td>3.1 (1.5 - 6.1)</td>
<td>7463</td>
</tr>
<tr>
<td>Current, ≥2 years cumulative use</td>
<td>30.3 (29.8 - 30.9)</td>
<td>2.3 (1.2 - 4.4)</td>
<td>7519</td>
</tr>
<tr>
<td>Past</td>
<td>17.7 (17.4 - 18.0)</td>
<td>1.5 (0.8 - 2.7)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Notes: Adapted from Tables 2 and 3 from N. Khan et al. Am J Gastroenterol 2021

* Unadjusted

Why is this important? Thiopurines (azathioprine, 6-mercaptopurine, and thioguanine) have been a mainstay of inflammatory bowel disease (IBD) treatment for decades. However, because they are only moderately effective as monotherapy and because of the growing availability of biologic and biosimilar agents, the future role of thiopurines for IBD treatment is uncertain. Furthermore, thiopurines are associated with multiple adverse effects of pancreatitis, non-melanoma skin cancer, lymphoma, and myelosuppression. Although myelosuppression is a known adverse event, no prior well-designed studies are available to estimate the risk of AML/MDS with thiopurines.
This rigorous study has several strengths which increase the likelihood of producing accurate and unbiased results:

- **Cohort**: The older age of the veteran cohort enhances the study's statistical power to detect a potential association between thiopurine use and AML/MDS because AML/MDS is more common in elderly individuals. Additionally, the algorithm used to identify veterans with IBD has previously been validated and demonstrated to have 95% positive predictive value\(^1\).

- **Exposure (thiopurine use)**: Because many veterans who receive healthcare through the Veterans Affairs Healthcare System also have pharmacy benefits, the investigators likely correctly identified thiopurine use.

- **Outcome (AML/MDS)**: The investigators validated all AML/MDS outcomes through chart review. Notably, only 107/344 patients identified with AML/MDS by administrative codes actually had AML/MDS subsequent to IBD. Other studies relying solely on administrative codes, such as studies using insurance claims data, could come to substantially different conclusions based on misclassification of the AML/MDS outcome.

**Key Study Finding**: Current thiopurine use is associated with a 2-3X increase in the risk of AML/MDS in IBD patients. However, since the baseline risk of AML/MDS is very low in IBD patients, there is only about one additional AML/MDS case per 7500 person-years of thiopurine use.

**Caution**: Observational research studies always come with the caveat that association does not equal causation. A major area of weakness for many observational studies is inadequate control of confounding. This occurs when the association between the exposure and the outcome is actually due to the association of each of these with a third condition, called a confounder. In this study, the authors controlled for confounding by several relevant demographic and medical variables such as age and biologic IBD medication exposure. Although the etiology of AML/MDS is largely idiopathic, the strongest identified risk factors are chemical exposures, prior chemo- and radiation therapy, and certain genetic abnormalities. The investigators accounted for these using the data on environmental and military toxin exposure available in the electronic health record, but these are likely under-recorded as these
confounders potentially occurred decades prior to thiopurine use. However, the impact of confounding by these factors are likely to be small as they probably do not influence whether a veteran with IBD receives a thiopurine or not. A second limitation is the lack of data on thiopurine metabolism. Because many of the adverse effects of thiopurines are mediated by metabolites\(^2\), stratification of the cohort by TPMT activity, TPMT genotype, or NUDT15 genotype\(^3\) may help determine if there are subpopulations of patients with IBD who are at higher risk for thiopurine-induced AML/MDS.

**My practice:** This rigorous study demonstrated a strong association between current thiopurine use and AML/MDS, which gives us pause when considering thiopurines for our patients—particularly the elderly and individuals with prior radiation exposure. However, since there is only one additional case per nearly 7500 person-years of thiopurine exposure, we individualize our decision-making and use combination therapy (e.g. thiopurine plus infliximab) if needed to control IBD disease activity while including this as a potential risk when educating IBD patients about risks of thiopurine therapy.

**For future research:** Based on the association of thiopurines with non-melanoma skin cancer, lymphoma\(^4\), and now AML/MDS plus the growing armamentarium of IBD medications, thiopurines may not be a major part of IBD therapy, especially for the elderly, in the near future.

**References**


