Effectiveness of Bile Acid Sequestrants in Microscopic Colitis and Utility of Bile Acid Testing: A Systematic Review and Meta-analysis

June Tome, MD[1], Raseen Tariq, MBBS[1], Cynthia J. Chelf, MLIS[2], Sahil Khanna, MBBS, MS, FACG[1] and Darrell S. Pardi, MD, MS, FACG[1]

INTRODUCTION: **Bile acid sequestrants (BAS) are an option for microscopic colitis (MC) refractory or intolerant to budesonide. There are inconsistent data on the prevalence of bile acid malabsorption (BAM) and utility of bile acid testing in MC. The aim of this systematic review and meta-analysis was to evaluate these outcomes.**

METHODS: **A systematic search of randomized control trials and observational studies of adults with MC treated with BAS was conducted using MEDLINE, Embase, Cochrane, and Scopus from inception to January 22, 2024. Data were extracted on (i) prevalence of BAM, (ii) clinical response and adverse events, and (iii) recurrence after BAS discontinuation. Data were pooled using random-effects models to determine weighted pooled estimates and 95% confidence intervals (CIs).**

RESULTS: **We included 23 studies (1 randomized control trial, 22 observational), with 1,011 patients with MC assessed for BAM and 771 treated with BAS. The pooled prevalence of BAM was 34% (95% CI 0.26–0.42, I^2 = 81%). The pooled response rate with BAS induction for all patients with MC, irrespective of BAM, was 62% (95% CI 0.55–0.70, I^2 = 71%). There was a higher pooled response rate in patients with BAM compared with those without BAM (P < 0.0001). The pooled rate of BAS-related adverse effects was 9% (95% CI 0.05–0.14, I^2 = 58%).**

DISCUSSION: **One-third of patients with MC had BAM, and almost two-thirds of all patients responded to BAS with limited side effects. Patients with MC and BAM were more likely to respond to therapy, supporting the value of bile acid testing.**

KEYWORDS: microscopic colitis; bile acid sequestrants; adverse effects; bile acid malabsorption

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D298.

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INTRODUCTION

Microscopic colitis (MC) is a frequent cause of chronic watery diarrhea and is composed of 2 subtypes, lymphocytic colitis (LC) and collagenous colitis (CC) that are distinguished by their histology (1,2). Both MC subtypes share similar clinical features, epidemiology, and overall response to treatment. Budesonide has been extensively studied in both clinical trials and observational studies for the treatment of MC. However, the risk of recurrence is high after the discontinuation of budesonide therapy, with a recent systematic review and meta-analysis demonstrating a pooled recurrence of 50% (95% confidence interval [CI] 0.38–0.63) (3). Therefore, many patients continue long-term budesonide, at the lowest effective dose, for maintenance therapy (4,5).

Bile acid sequestrants (BAS) are a treatment option for patients with MC who are refractory or intolerant to budesonide, as well as those that prefer to avoid long-term corticosteroid use. Although the pathophysiology of MC is not well established, bile acid malabsorption (BAM) has been postulated as a potential mechanism (6,7). BAS (e.g., cholestyramine, colesevelam, and colestipol) may consequently present an alternative treatment strategy for a subgroup of patients with MC. Although assessing for bile acid diarrhea is not part of the standard diagnostic workup for MC, testing may be considered in patients who do not respond to budesonide. The 2016 American College of Gastroenterology guidelines do not offer guidance on the use of BAS monotherapy for MC because of lack of sufficient evidence (8). The 2021 European guidelines

[1]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA; [2]Mayo Clinic Libraries, Mayo Clinic, Rochester, Minnesota, USA.
Correspondence: Darrell S. Pardi, MD, MS. E-mail: pardi.darrell@mayo.edu.
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suggest treatment with BAS for patients with MC and concurrent BAM, citing a low level of evidence for this recommendation (9).

Since the development of these guidelines, newer studies have emerged evaluating clinicals outcomes of BAS therapy for MC (10,11). However, there are inconsistent data on clinical response and adverse effects with BAS treatment, and most studies are limited to small patient cohorts. The role of BAM testing and the use of BAS as a treatment strategy for MC thus warrants further investigation. The aim of this systematic review and meta-analysis was to evaluate the prevalence of BAM and the utility of bile acid testing for predicting response to BAS therapy in MC.

METHODS

Data sources and search strategy

This meta-analysis was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (12). A comprehensive search of several databases was conducted on July 13, 2023, and updated on January 22, 2024, with the results limited to English Language. Databases searched were MEDLINE, Embase, Cochrane, and Scopus without any date limits. The search strategies were developed and performed by a medical librarian with consultation from the study investigators. The detailed strategies of all used search terms are available in Supplementary Table 1 (see Supplementary Digital Content 1, http://links.lww.com/AJG/D298).

Study selection and data abstraction

Two investigators (J.T. and R.T.) independently screened all titles and abstracts for pertinent randomized control trials (RCTs), case-control, cohort studies, and case-series relating to clinical outcomes with BAS therapy and/or BAM testing in adults with MC. Exclusion criteria included (i) patients without biopsy-proven MC, (ii) patients with incomplete MC on histology, (iii) pediatric population, (iv) case series with less than 5 patients or case reports of individual patient outcomes, and (v) insufficient data on BAM testing and/or treatment response to BAS. Studies presented only in abstract form at national conferences that met all selection criteria were included. No studies were excluded based on the type of BAM testing, length of BAS therapy, nor the period of follow-up time after completion of treatment. A full-text review was subsequently conducted for all studies achieving the eligibility criteria.

Data was extracted on primary outcomes: (i) prevalence of BAM (diagnosed via serum 7-α-hydroxy-4-cholesten-3-one, fecal bile acids, or ^{75}Selenium homotaurocholic acid test [SeHCAT]), (ii) clinical response and adverse events with BAS, and (iii) clinical recurrence after drug discontinuation. Secondary outcomes included response to BAS by MC subtype. The data extraction was conducted separately by 2 investigators (J.T. and R.T.), and any differences were settled by shared discussion or evaluation with a senior reviewer (D.S.P) referring to the original study. To determine possible sources of heterogeneity related to the prevalence of BAM in MC, preplanned subgroup analyses were conducted based on the modality used for testing.

Study quality assessment

All studies were critically assessed independently by 2 investigators (J.T. and R.T). For the 1 included RCT, the Cochrane Risk of Bias Tool was used to evaluate the risk of bias (see Supplementary Table 2, Supplementary Digital Content 1, http://links.lww.com/AJG/D298). The Cochrane Tool appraises RCTs by 6 criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting (13). The quality of cohort studies without a control group was measured using the Joanna Briggs Institute (JBI) Critical Appraisal Tool (see Supplementary Table 3, Supplementary Digital Content 1, http://links.lww.com/AJG/D298). JBI appraises studies in 9 specific domains: study sample frame, participant sampling, sample size, study subjects and setting, data analysis coverage of identified sample, methods for identification of condition and application to all participants, statistical analysis, and response rate (14).

Statistical analyses

In our combined analysis, we focused on measuring the rates of response and recurrence using BAS. To estimate the weighted pooled resolution rate, we applied the random-effects model formulated by DerSimonian and Laird (15). The WPR, along with its 95% CI, was calculated for both the overall and subgroup analyses. The size of each study's sample was used as a weighting factor in determining the weighted pooled resolution rate. To evaluate the heterogeneity within the groups, we used the I^2 statistic. This statistic helps in identifying the percentage of variation across studies attributable to differences in patients, study design, or interventions, as opposed to random chance (16). An I^2 value over 50% indicates a high level of heterogeneity. We considered P values less than 0.05 as statistically significant for all our tests, except when assessing heterogeneity. The presence of publication bias was examined using the Luis Furuya-Kanamori (LFK) index on a Doi plot. The graphs and data representations were created using MetaXL 5.3 software by Epigear.

RESULTS

Search results and characteristics of included studies

A total of 259 potentially relevant publications were identified, 45 passed abstract screening, and 23 studies (1 RCT and 22

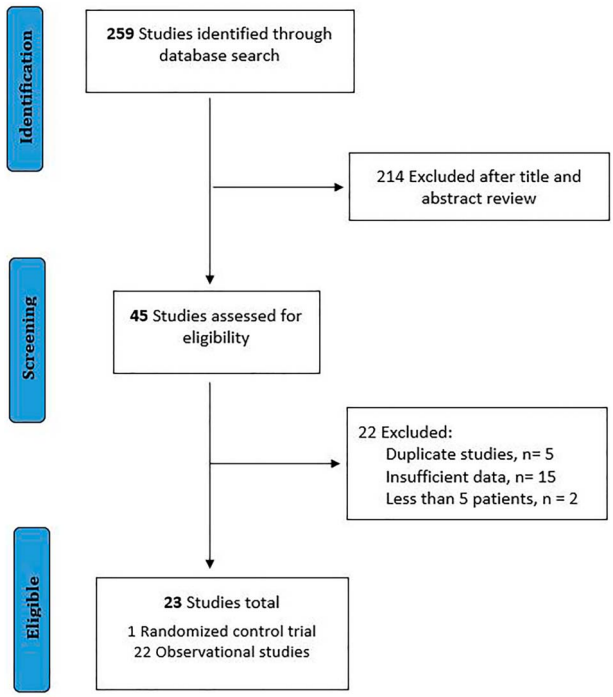

Figure 1. Flow diagram of study selection for systematic review and meta-analysis.

Table 1. Characteristics of the included MC studies

Study (year)	Location	Study design	MC subtype	Clinical response definition	Study timeframe/ follow-up	BAS type/dose (daily)	BAM testing
Baert et al, 2004 (17)	Belgium	Retrospective cohort	LC	Complete resolution of diarrhea	Mean follow-up 2 yr (range 0.5–5)	Cholestyramine 4–12 g/d	N/A
Bajor et al, 2006 (18)	Sweden	Prospective cohort	CC	N/A	8 wk	N/A	^{75}SeHCAT (retention values <10% on day 7)
Bjornback et al, 2011 (19)	Denmark	Retrospective cohort	Both	Patient report of normalized stool consistency and frequency	1999–2010	Cholestyramine; dose not reported	^{75}SeHCAT (retention <15% on day 7)
Bohr et al, 1996 (20)	Sweden	Retrospective cohort	CC	Patient report of improvement in diarrhea	1989–1995, median follow-up 3 yr	Cholestyramine; dose not reported	^{75}SeHCAT (retention <10% on day 7)
Brydon et al, 2011 (21)	Scotland	Prospective cohort	Both	N/A	3 yr	N/A	Serum C4 (>30 ng/mL)
Calabrese et al, 2007 (22)	Italy	RCT	Both	Complete resolution of diarrhea	1998–2003, mean follow-up 44.9 mo	Cholestyramine 4 g/d	N/A
Collussi et al, 2015 (23)	United States	Retrospective cohort	Both	Complete resolution of diarrhea (<3 stools per day)	2002–2013, minimum 2 follow-up appointments	Cholestyramine; dose not reported	N/A
Fernandez-Banares et al, 2001 (24)	Spain	Prospective cohort	Both	Complete resolution of diarrhea (<3 formed or semiformed stools per day)	Mean follow-up 24.9 mo (range 8–44)	Cholestyramine 2–12 g/d	^{75}SeHCAT (retention <11% on day 7)
Fernandez-Banares et al, 2003 (25)	Spain	Prospective cohort	Both	Complete resolution of diarrhea (<3 formed or semiformed stools per day)	1992–2001, mean follow-up 36.9 mo (range 6–96)	Cholestyramine 2–12 g/d	^{75}SeHCAT (retention <11% on day 7)
Kamboj et al, 2022 (26)	United States	Retrospective cohort	Both	<3 stools per day	2007–2008 and 2011–2013	Not reported	N/A
Lim et al, 2019 (27)	United Kingdom	Retrospective cohort	Both	N/A	2012–2016	N/A	^{75}SeHCAT (retention <15% on day 7)
Lyutakov et al, 2021 (28)	Bulgaria	Prospective cohort	Both	N/A	2017–2020	N/A	Serum C4 (>48.3 ng/mL)
Munch et al, 2011 (29)	Sweden	Prospective cohort	CC	N/A	2005–2009	N/A	^{75}SeHCAT (retention <10% on day 7)
Northcutt et al, 2022 (10)	United States	Retrospective cohort	Both	<3 stools per day and <1 watery stool per day	2004–2018, median follow-up 35 mo	Cholestyramine 4 g 1–2 times per day; colestipol	N/A

Table 1. (*continued*)

Study (year)	Location	Study design	MC subtype	Clinical response definition	Study timeframe/ follow-up	BAS type/dose (daily)	BAM testing
						2 g/d; colesevelam 625 mg 1–2 times per day	
Olesen et al, 2004 (30)	Sweden	Retrospective cohort	LC	Patient report of improvement in diarrhea	Median follow-up 13 mo	Cholestyramine; dose not reported	^{75}SeHCAT (retention <10% on day 7)
Pardi et al, 2002 (31)	United States	Retrospective cohort	LC	Complete resolution of diarrhea	1997–1999, median follow-up 12 mo	Cholestyramine; dose not reported	N/A
Saha et al, 2020 (32) [Abstract]	United States	Prospective cohort	Both	<3 stools per day and <1 watery stool per day	Not specified, data collected 8 d after treatment	Colesevelam 625 mg 3 tablets b.i.d.	Serum C4 (cutoff value not reported)
Tome et al, 2023 (11)	United States	Retrospective cohort	Both	Complete resolution of diarrhea (<3 stools per day)	2010–2020, median follow-up 4.5 yr	Cholestyramine mean 8.1 g/d; colesevelam 3.2 g/d; colestipol 4.3 g/d	48-hr fecal bile acid collection and/or serum C4 (total BA >2,337 μmol/48 hr; primary BA >10%, or primary BA >4% with total BA >1,000 μmol/48 hr)
Trimble et al, 2016 (33) [Abstract]	United Kingdom	Retrospective cohort	CC	N/A	2000–2015	N/A	Serum C4 (cutoff value not reported)
Ung et al, 2000 (34)	Sweden	Retrospective cohort	CC	<3 stools per day	36 mo	Median dose 2.5 packets per day; cholestyramine 4-g packet or colestipol 5-g packet	^{75}SeHCAT (retention <10% on day 7)
Ung et al, 2002 (35)	Sweden	Prospective cohort	LC	<3 stools per day	48 mo	Cholestyramine 4-g packet or colestipol 5-g packet initiated b.i.d.-t.i.d.	^{75}SeHCAT (retention <10% on day 7)
Vijayvargiya et al, 2022 (36)	United States	Retrospective cohort	Both	Physician or patient reported improvement in diarrhea	2–24 mo	Not reported	48-hr fecal bile acid collection (>2,337 μmol total bile acids/48 hr) or elevated primary fecal bile acids (>10% primary bile acids or > 4% primary bile acids + > 1,000 μmol total bile acids/48 hr)
Wildt et al, 2003 (37)	Denmark	Retrospective cohort	Both	>25% reduction in bowel frequency	1997–2001	Cholestyramine 2–18 g/d	^{75}SeHCAT (retention <15% on day 7)

BA, bile acid; BAM, bile acid malabsorption; BAS, bile acid sequestrant; CC, collagenous colitis; LC, lymphocytic colitis; MC, microscopic colitis; N/A, not available; RCT, randomized control trial; SeHCAT, selenium homotaurocholic acid test.

observational) were included (Figure 1). These 23 studies comprised 1,011 patients with MC assessed for BAM and 771 patients treated with BAS therapy. The characteristics of the studies including the study design, MC subtype, method of BAM testing with diagnostic cutoff values, the type/dose of BAS therapy, and the duration of follow-up are presented in Table 1. Two of the included studies were only presented in abstract form (32,33).

Quality of included studies

The quality of the included studies for the RCT and the observational studies is displayed in Supplementary Tables 2 and 3 (see Supplementary Digital Content 1, http://links.lww.com/AJG/D298). The 1 RCT included in this systematic review and meta-analysis did not blind participants or personnel. In addition, the clinical trial lacked a placebo group. The main limitations for observational studies assessed using the JBI appraisal tool included small cohort size in 5 studies, and 5 studies did not appropriately specify how clinical response to BAS therapy was defined.

Primary outcomes

Prevalence of BAM. A total of 16 studies were included, with 1,011 patients with MC assessed for BAM (median age of 61 years and 80.1% women). The overall pooled prevalence of BAM in MC was 34% (95% CI 0.26–0.42, $I^2 = 81\%$) (Figure 2) with ^{75}SeHCAT, the most used test for BAM diagnosis. No publication bias was observed on the Doi plot for all included studies, with an LFK index of 0.07 (see Supplementary Figure 1, Supplementary Digital Content 1, http://links.lww.com/AJG/D298). A total of 5 studies used serum C4 testing with an overall pooled prevalence of BAM in MC of 40% (95% CI 0.18–0.65, $I^2 = 92\%$), and 11 studies used ^{75}SeHCAT testing with an overall pooled prevalence of 31% (95% CI 0.24–0.38, $I^2 = 62\%$). Only 1 of the included studies used 48-hour fecal bile acid collection to assess for BAM in MC, in addition to serum C4 testing (11).

Clinical outcomes with BAS. A total of 16 studies were included, with 771 patients with MC treated with BAS induction therapy. The pooled clinical response rate with BAS induction therapy for all patients with MC, irrespective of BAM, was 62% (95% CI 0.55–0.70, $I^2 = 71\%$) (Figure 3). No publication bias was observed on the Doi plot for all included studies, with an LFK index of −0.71 (see Supplementary Figure 2, Supplementary Digital Content 1, http://links.lww.com/AJG/D298). The type of BAS and dose of therapy in each study is displayed in Table 1. Cholestyramine was the most prescribed BAS; the dose ranged from 2 to 18 g/d. The overall pooled clinical response rate with cholestyramine therapy was 63% (95% CI 0.52–0.74, $I^2 = 76\%$). The clinical response rate with colestipol and colesevelam therapy could not be separately pooled with the data reported in the included studies.

A total of 6 studies, including 260 patients, evaluated clinical outcomes with BAS therapy based on the presence or absence of BAM. The pooled clinical response rate in those with BAM was 71% (95% CI 0.58–0.84, $I^2 = 64\%$) compared with 39% (95% CI 0.19–0.62, $I^2 = 78\%$) without BAM ($P < 0.0001$). Mild asymmetry was seen on the Doi plot in those with and without BAM, with an LFK index of 1.38 and −1.90, respectively.

Adverse effects. Ten studies comprising 527 patients reported adverse events on BAS therapy with a pooled rate of BAS-related adverse effects of 9% (95% CI 0.05–0.14, $I^2 = 58\%$) (Figure 4). The most frequent side effects included nausea, dyspepsia, and headache. Mild asymmetry was observed on the Doi plot, with LFK index of 1.05 (see Supplementary Figure 3, Supplementary Digital Content 1, http://links.lww.com/AJG/D298). None of the included observational studies or the RCT contained a placebo group for comparison.

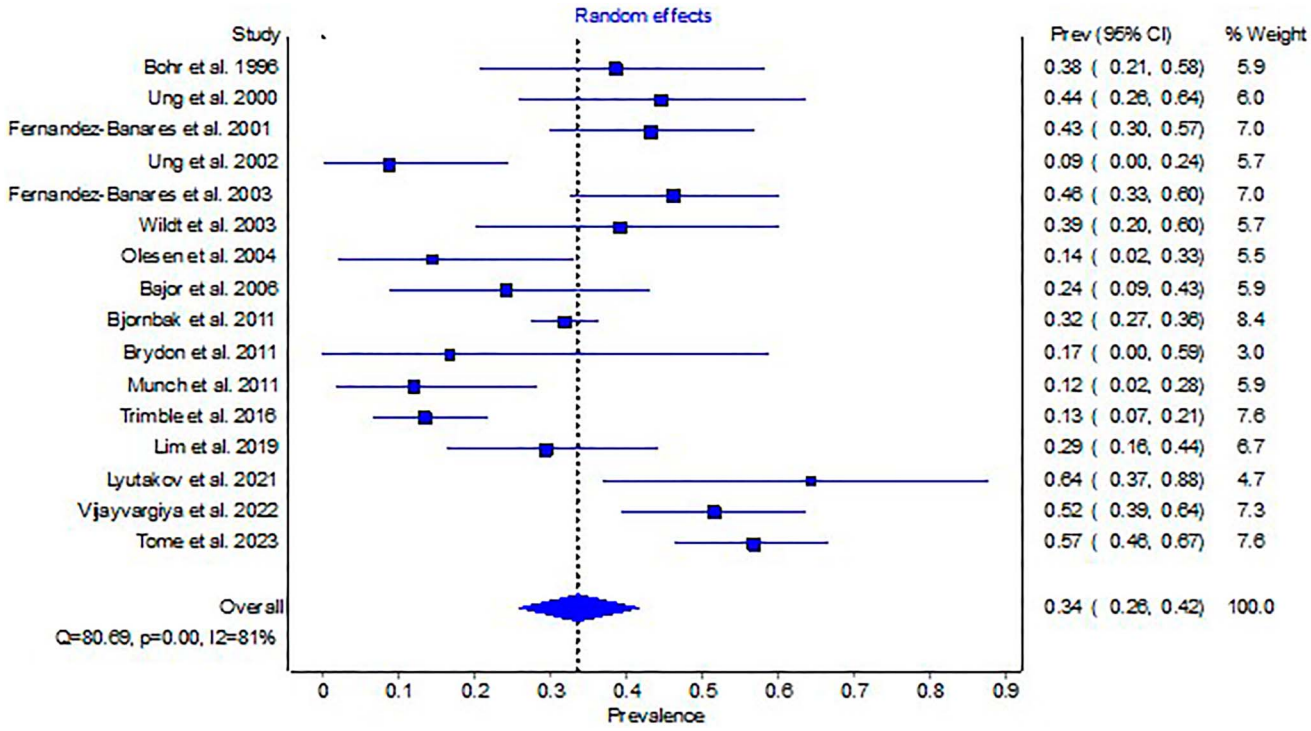

Figure 2. Prevalence of bile acid malabsorption in microscopic colitis. CI, confidence interval.

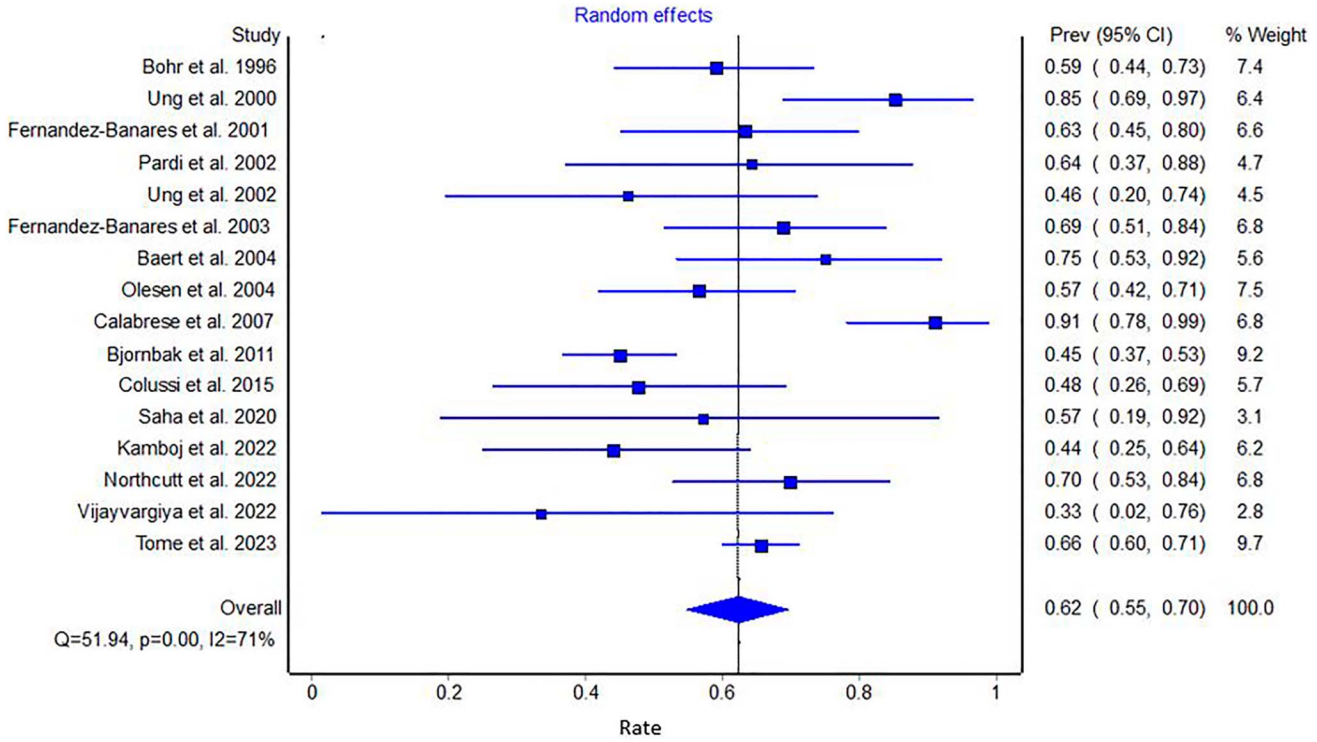

Figure 3. Effectiveness of bile acid sequestrant therapy in microscopic colitis. CI, confidence interval.

Recurrence after BAS discontinuation. Only 2 studies evaluated both the rate of recurrence after BAS discontinuation (11,22) and the clinical response with BAS maintenance therapy (10,11). Among 239 patients, the rate of recurrence was 35.1% after the discontinuation of BAS therapy. The clinical response rate in 88 patients with BAS maintenance therapy was 71.6%. Both studies (10,11) additionally reported BAS as a maintenance strategy for budesonide-dependent patients; 65.9% were able to taper their maintenance dose of budesonide, and 33.7% were able to completely discontinue budesonide. Weighted pooled estimates could not be calculated because of the limited number of studies assessing these endpoints.

Secondary outcomes

Clinical response by MC subtype. Seven studies consisting of 352 patients evaluated BAS response in CC with an overall pooled clinical response rate of 65% (95% CI 0.49–0.80, I^2 = 87%) (Figure 5a). Nine studies comprising 318 patients evaluated BAS outcomes in LC with an overall pooled clinical response rate of 65% (95% CI 0.57–0.72, I^2 = 42%) (Figure 5b). There was no significant difference in response to BAS therapy between MC subtypes (P = 1.00). Mild asymmetry was seen on the Doi plot in those with CC and LC, with an LFK index of 1.43 and 1.79, respectively (see Supplementary Figures 4A and B, Supplementary Digital Content 1, http://links.lww.com/AJG/D298).

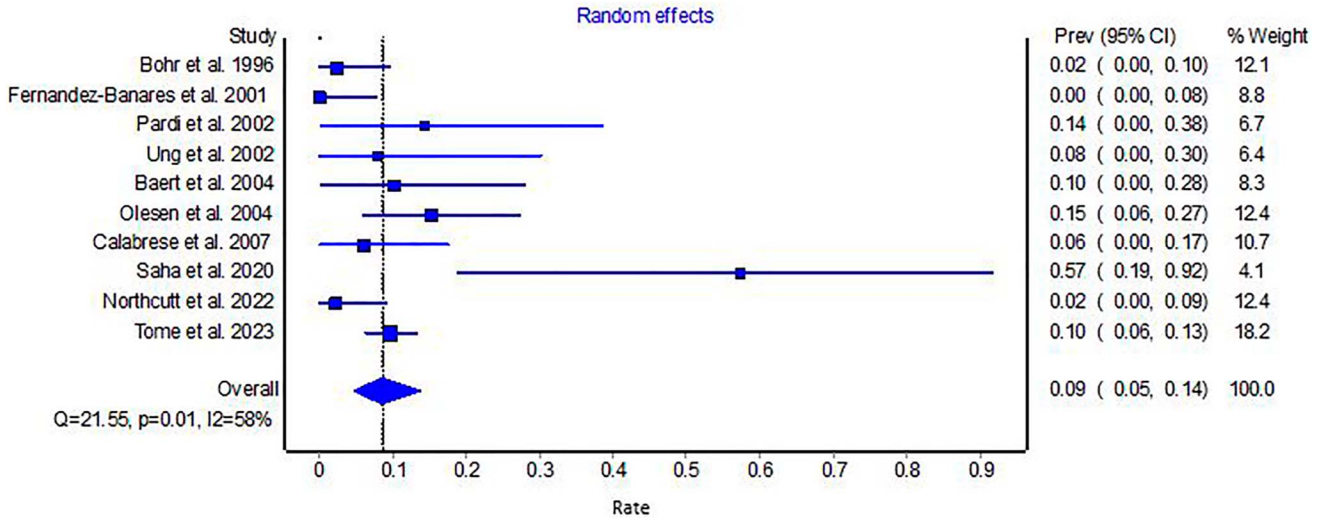

Figure 4. Adverse effects with bile acid sequestrant therapy. CI, confidence interval.

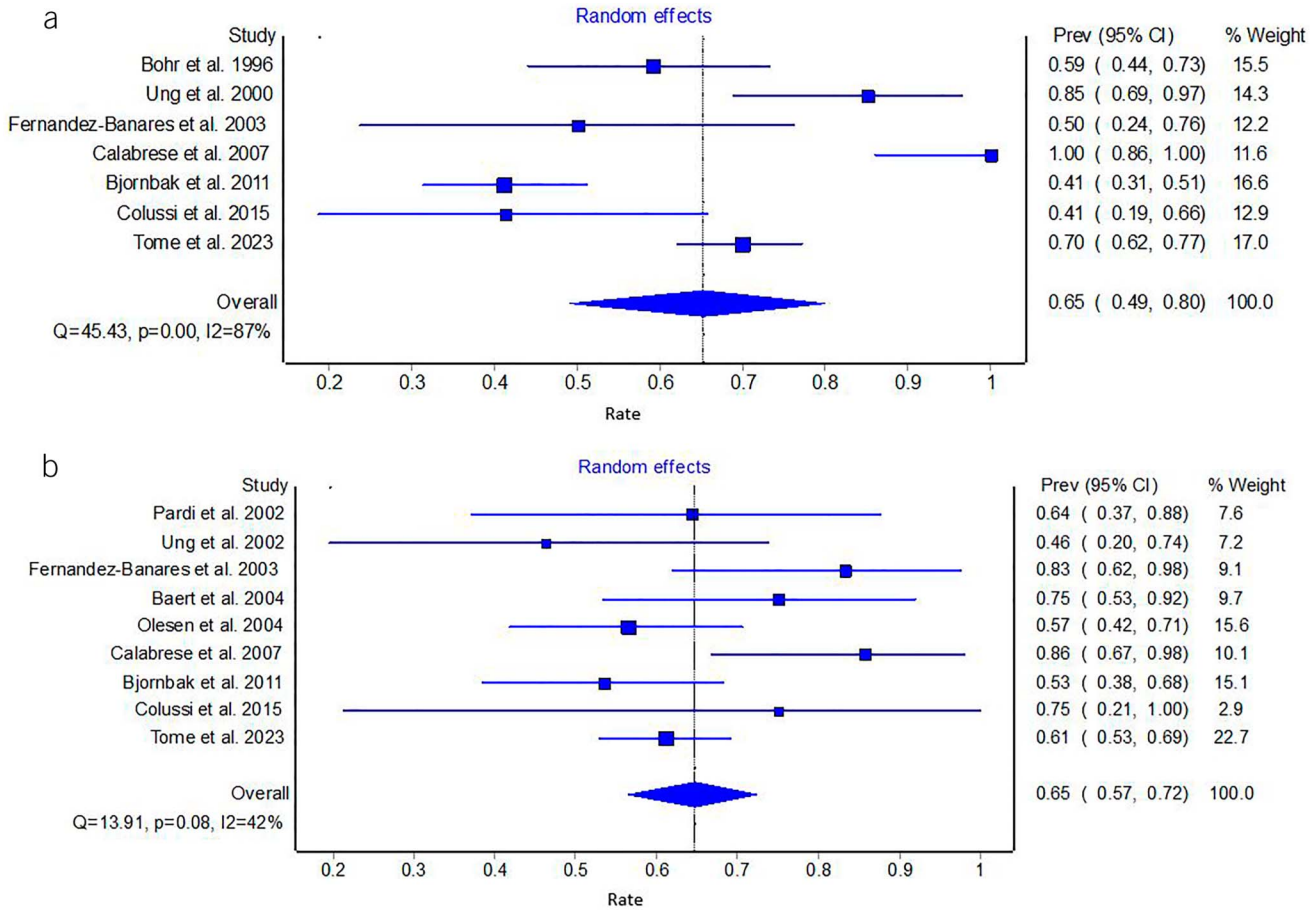

Figure 5. (**a**) Effectiveness of bile acid sequestrant therapy for collagenous colitis. (**b**) Effectiveness of bile acid sequestrant therapy for lymphocytic colitis. CI, confidence interval.

DISCUSSION

Although budesonide remains the first-line treatment for MC in patients with moderate to severe disease (8,9), there is significant variation in the management of patients that are refractory or intolerant to treatment. In addition, there is significant variation in the treatment approach for the subgroup of patients who prefer an alternative to long-term corticosteroids for maintenance therapy. In this large systematic review and meta-analysis, almost two-thirds of all patients responded to BAS with no significant differences in response between MC subtypes. This suggests that BAS are an effective treatment option for the management of MC.

In addition, there is a relatively high prevalence of BAM in patients with MC. In this meta-analysis, about one-third of all patients with MC had BAM, and those with MC and BAM were more likely to respond to BAS therapy, supporting the utility of bile acid testing in predicting response to treatment, particularly in patients who do not respond to budesonide. The use of BAS therapy should be considered for those with concomitant MC and BAM, although our results suggest that more than a third of patients with MC without BAM still appear to respond to this therapy.

This meta-analysis also demonstrates that BAS therapy is relatively well-tolerated with limited adverse effects. BAS treatment is thus an attractive option in patients with refractory MC, even in those without coexistent BAM, given its overall tolerability with limited side effects compared with other options such as immunosuppression or biologics (38). Advantages of BAS therapy include the safety profile, relative decreased cost, and ease of administration compared with immunosuppressive or biologic therapy (39). Patients on long-term BAS therapy should be educated on the risk of (and monitored for) deficiency of fat-soluble vitamins as well as potential drug interactions.

To the best of our knowledge, this is the largest systematic review and meta-analysis assessing the prevalence of BAM in MC as well as the effectiveness of BAS treatment. Strengths of this meta-analysis are the extensive literature review presenting data from all available publications studying the prevalence BAM in MC and clinical outcomes with BAS therapy, the clear inclusion criteria, as well as the rigorous appraisal of each study quality. The main limitations are the heterogeneity among studies because of the differences in protocol design with BAS type, dose, and duration. Referral bias is another potential limitation because most studies were conducted at large academic centers and may overestimate the prevalence of BAM. Studies varied in the method used to assess for BAM in MC as well as the diagnostic cutoff values. The ^{75}SeHCAT test is predominantly used in Europe, whereas the 48-hour fecal bile acid collection (total and primary bile acids) and fasting serum C4 tests are primarily used in the United States (40). Although each of these tests has its own advantages and drawbacks, they have all been studied for the evaluation of bile acid diarrhea (41).

In conclusion, this meta-analysis suggests that BAS is an effective therapy for patients with MC. Almost two-thirds of all

patients responded to BAS with limited side effects. In addition, patients with MC and BAM were more likely to respond to BAS therapy, supporting the role of bile acid testing in helping predict response to treatment. As most of the current literature evaluating BAS therapy in MC consists of observational studies, future controlled studies are needed to better assess optimal dosing, patient selection, the rate of recurrence after drug discontinuation, and the role of BAS for maintenance therapy.

CONFLICTS OF INTEREST

Guarantor of the article: Darrell S. Pardi, MD, MS, FACG.
Specific author contributions: J.T., R.T., and D.S.P.: research area and study design. J.T. and R.T.: data acquisition. J.T., R.T., and D.S.P.: data analysis and interpretation. R.T.: statistical analysis. S.K. and D.S.P.: supervision or mentorship.
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