TITLE: Controversies in inflammatory bowel disease: exploring clinical dilemmas using Cochrane reviews.

RUNNING HEAD: Exploring clinical dilemmas in IBD

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ABBREVIATIONS:

ABSTRACT:

A symposium organized by the Cochrane IBD Group and presented at the 2017 Digestive Disease Week annual meeting reviewed the recent literature on several controversial topics in inflammatory bowel disease (IBD) management: the efficacy of oral aminosalicylates for induction and maintenance of Crohn's disease (CD); the feasibility of drug withdrawal in patients with quiescent CD; and strategies for detecting colon cancer in patients with IBD. This article summarizes the data presented at that session.

Keywords: Crohn's disease, ulcerative colitis, drug therapy, cancer detection, colonoscopy

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INTRODUCTION

Substantial advances have been made in inflammatory bowel disease (IBD) therapeutics during recent years, however, gastroenterologists continue to be confronted with challenging clinical scenarios. This article highlights new findings from Cochrane reviews regarding controversial IBD management strategies with the goal of facilitating evidence-based decision-making.

ORAL AMINOSALICYLATES FOR THE TREATMENT OF CROHN'S DISEASE

Data supporting the use of oral aminosalicylates for the treatment of Crohn's disease (CD) first emerged approximately four decades ago with the National Co-operative Crohn's Disease Study (NCCDS) and European Co-Operative Crohn's Disease Study (ECCDS).(1, 2) These early randomized controlled trials (RCTs) established sulfasalazine as an effective, safe and inexpensive therapy in patients with mild-to-moderate CD. The discovery of 5-aminosalicylic acid (5-ASA) as the therapeutically active metabolite of sulfasalazaine ultimately led to the development of sulfa-free 5-ASA formulations designed to deliver high-dose drug concentration without sulfasalazine-associated side effects.(3)

Population-based cohort studies reveal that orally-administered aminosalicylates (5-ASA 3.2 to 4.0 g or sulfasalazine 3.0 to 6.0 g daily) are the most commonly prescribed therapy for CD, with approximately 60% of all patients having received these drugs at some point during their disease course.(4-6) A retrospective database analysis of prescription rates among elderly patients with IBD showed that while aminosalicylate prescriptions for CD tapered between 2004 and 2009 in Canada (~70% to 60%) and Denmark (~60% to 40%), prescription rates have remained stable in the United States and United Kingdom.(7)

The continued use of aminosalicylates for the treatment of CD is concerning for several reasons. First, administering aminosalicylates as first-line therapy might delay the initiation of more potent, effective therapies and consequently increase the risk of disease-related complications. While the conventional step-up model involves sequentially treating patients with antibiotics or aminosalicylates, corticosteroids, immunosuppressants, biologics and surgery based on response status, findings from two large RCTs indicates that early intensive treatment (i.e. “top-down therapy”) may have the greatest potential to modify the natural course of CD in high-risk patients.(8, 9) Second, and most importantly, efficacy data regarding the use of aminosalicylates for the treatment of CD are conflicting.(10, 11) Third, while aminosalicylates are associated with a relatively favorable safety profile, the possibility of developing rare but serious adverse events such as interstitial nephritis, pleuritis, myopericarditis and pancreatitis exists.(12) Although aminosalicylates are safe and inexpensive, these benefits may be outweighed by their questionable efficacy in CD.

Efficacy of aminosalicylate induction therapy

A Cochrane review conducted by Lim et al evaluated 20 RCTs (N = 2367) that compared aminosalicylates to placebo, corticosteroids and other aminosalicylates for induction of remission in adult patients with mild-to-moderate CD.(10)

The NCCDS and ECCDS compared sulfasalazine, corticosteroids and placebo, and reported on clinical remission rates (defined as a Crohn's Disease Activity Index [CDAI] score <150) at weeks 17 and 18, respectively.(1, 2) When data were combined, a non-statistically significant trend in favour of sulfasalazine was observed (sulfasalazine: 45%, 63/141; placebo: 29%, 43/148; risk ratio [RR] 1.38, 95% confidence interval [CI] 1.00 to 1.89, p = 0.05), with the treatment benefit most pronounced in patients with colonic disease. There were no statistically significant between-group differences in adverse event, serious adverse event and withdrawal due to adverse event rates. Sulfasalazine was less effective than corticosteroids, with 43% (55/128) of sulfasalazine-treated patients entering clinical remission compared to 60% (79/132) of corticosteroid-treated patients (RR 0.68, 95% CI 0.51 to 0.91, p = 0.009), however sulfasalazine was associated with fewer adverse events (RR 0.43, 95% CI 0.22 to 0.82, p = 0.01). The quality of evidence supporting these outcomes was considered moderate due to sparse data.

Three RCTs compared low-dose, controlled-release 5-ASA (Pentasa® 1.0 to 2.0 g/day) to placebo.(13-15) A total of 38% (79/205) of patients receiving active therapy had clinical improvement compared to 35% (48/137) of placebo patients, demonstrating a non-statistically significant benefit in favor of 5-ASA (RR 1.07, 95% CI 0.8 to1.42, p = 0.65). The overall quality of evidence was rated as low due to incomplete outcome data and sparse data. Adverse event and withdrawal due to adverse event rates in the 5-

ASA and placebo groups were similar (28% [58/205] and 23% [31/135], respectively; RR 1.33, 95% CI 0.91 to 1.96, p = 0.14).

High-dose, controlled-release 5-ASA (Pentasa® 4.0 g/day) versus placebo was assessed in three studies.(13, 16, 17) The pooled analysis revealed a mean difference (5-ASA – placebo) in CDAI reduction of -19.8 points, however this trend was neither statistically significant (95% CI -46.2 to 6.7, p = 0.14) nor clinically meaningful.(18, 19)

Olsalazine, an azo-bonded pro-drug, was found to be statistically inferior to placebo for induction of clinical response or remission in a single RCT (RR 0.36, 95% CI 0.18 to 0.71, p = 0.004). Furthermore, a substantial proportion of the patients receiving active therapy withdrew due to diarrhea (22% versus 4% of placebo patients, p = 0.015).(20)

A pH-dependent, delayed-release 5-ASA drug (Asacol® 3.2 g/day) was compared to placebo in one study. The majority (60%, 12/20) of patients receiving this formulation achieved clinical response or remission versus 22% (4/18) of placebo patients (RR 2.70, 95% CI 1.06 to 6.88, p = 0.04). However, the proportion of patients who achieved clinical remission was not statistically significant (5-ASA: 45%, 9/20; placebo: 4/18, 22%, RR 2.02, 95% CI 0.75 to 5.45, p = 0.16). The quality of evidence for these outcomes was rated as very low due to incomplete outcome data and very sparse data. There was no statistically significant between-group difference in adverse event rates (5-ASA: 80%, 16/20; placebo: 90%, 18/20; RR 0.90 95% CI 0.69 to 1.18, p = 0.45).

Delayed-release 5-ASA formulations (Salofalk® 3.0 to 4.5 g/day or Asacol® 4.0 g/day) were not found to be more effective than corticosteroids (6-methylprednisolone 40 to 48 mg/day or prednisone 40 mg/day).(21-23) Clinical remission was achieved in 57% (58/102) of 5-ASA patients compared to 53% (40/76) of corticosteroid patients (RR 1.04, 95% CI 0.79 to 1.36, p = 0.79). The overall quality of evidence for this outcome was moderate. Adverse event, serious adverse event and withdrawal due to adverse event rates were similar across treatment groups.

Two RCTs compared controlled-release (Pentasa®) or delayed-release 5-ASA (Salofalk®) to budesonide. Results from these studies were not pooled for analysis. Pentasa® was statistically inferior to Entocort® 9.0 mg/day for induction of remission (34% [30.89] versus 60% [56/93], respectively; RR 0.56, 95% CI 0.40 to 0.78, p <0.001).(24) The evidence supporting this outcome was low due to incomplete outcome data and sparse data. While adverse event and serious adverse event rates were similar across treatment groups, significantly more 5-ASA patients withdrew due to adverse events, with most of these events related to worsening disease activity. (Pentasa®: 39% (35/89), budesonide: 14% 13/93; RR 2.81, 95% CI 1.60 to 4.96, p < 0.001). Moderate quality evidence from one study failed to demonstrate a statistically appreciable difference in clinical remission rates between patients treated with Salofalk® and Budenofalk® (62% [95/153] versus 69% [107/154], respectively; RR 0.89, 95% CI 0.76 to 1.05, p = 0.17).(25) Budesonide was suggested by the authors as the preferred choice in patients with more severe inflammation including those with a relatively high erythrocyte sedimentation rate, C-reactive protein concentration or

baseline CDAI score. Adverse event rates were similar in the budesonide and 5-ASA groups.

Efficacy of aminosalicylate maintenance therapy

A Cochrane review by Akobeng et al identified 12 RCTs (N = 2146) comparing aminosalicylates to placebo for maintenance of medically-induced remission in CD.(11) None of the included studies assessed sulfasalazine as a maintenance therapy. At 12 months, 53% (526/998) of patients treated with 5-ASA (1.6 to 4.0 g/day) relapsed compared to 54% of placebo patients (544/1016) (RR 0.98, 95% CI 0.91 to 1.07, p = 0.70). The evidence supporting this outcome was of moderate quality due to sparse data. There was also no statistically significant difference between active therapy and control with respect to relapse rates at 12 months among pediatric patients. Adverse event, withdrawal due to adverse event and serious adverse event rates were similar in the 5-ASA and placebo groups.

Summary

Most guidelines(26, 27) do not recommend oral aminosalicylates for the treatment of CD given that this drug class is potentially 1) no more effective than placebo and inferior to corticosteroids for induction of response or remission; and 2) ineffective as a maintenance agent among patients with medically-induced remission. Despite this, oral aminosalicylates continue to be frequently prescribed.

Several factors may contribute to the disconnect between the evidence base and the use of oral aminosalicylates as a CD therapy in clinical practice. One possibility is that the quality of evidence from existing RCTs has failed to adequately convince

physicians that these drugs are ineffective in CD. The number of studies and data are limited, and most of the trials summarized above are 20 to 30 years old. The patient populations are heterogenous due to variable entry criteria, and blinded endoscopic eligibility and outcome assessments were not performed. Furthermore, the maintenance trials included primary non-responders, as opposed to contemporary maintenance trials of biologics in which only responders are eligible for participation. A second option is that oral aminosalicylates have a true protective effect in patients with CD and as such these medications continue to be prescribed by physicians. A prediction model based on the REACT study found that 5-ASA use was inversely related to need for surgery in univariate and multivariate analysis.(28) Finally, it may be that a substantial proportion of CD patients receive oral aminosalicylates because physician attitudes have failed to change prescribing behavior despite evidence to suggest that these drugs are ineffective.

An actively recruiting, pragmatic, open-label, randomized, non-inferiority trial (Stopping Aminosalicylate Therapy in Crohn's Disease [STATIC]; NCT03261206) in which patients with quiescent CD will be randomized to either continue to or discontinue oral aminosalicylates is currently underway. Results from this study are expected to provide further evidence regarding the efficacy of these drugs in CD.

WITHDRAWAL OF DRUG THERAPY IN PATIENTS WITH INACTIVE CROHN'S DISEASE

Adoption of the top-down and combination therapy(29) approaches, coupled with an enhanced emphasis on mucosal healing(30), has resulted in early and lengthened administration of immunosuppressants and biologic agents in high-risk IBD patients. While these treatment strategies are effective, there are safety and cost concerns regarding prolonged exposure to thiopurines (i.e. 6-mercaptopurine [6-MP] and azathioprine [AZA]), methotrexate [MTX] and monoclonal antibodies (i.e. adalimumab, infliximab, certolizumab pegol, vedolizumab and ustekinumab).

Observational data suggest that continued thiopurine use is linked to the development of lymphoproliferative disorders(31), and cancer of the skin and urinary tract.(32, 33) MTX-induced immunosuppression may result in elevated liver enzymes, and in rare cases, hepatotoxicity.(34) Thus, it is recommended that regular liver chemistries, creatinine testing and complete blood counts be performed pre- and post-MTX initiation.(35)

Tumor necrosis factor-alpha (TNF-α) antagonist therapy may be associated with heightened susceptibility to infection(36), and there is conflicting evidence about a potential for increased melanoma risk.(37, 38) Adverse event data on the extended use of anti-IL 12/23 (ustekinumab) and anti-integrin (vedolizumab) therapy in CD is particularly lacking. In addition to having an uncertain long-term safety profile, biologic medications are relatively expensive, representing approximately 65% of the direct treatment costs of CD.(39)

Pharmacologic reduction or cessation in CD patients who have attained extended remission is an important issue for patients, health-care providers, policy-makers and

payers to consider. Drug de-escalation may offer safety and cost benefits, or alternatively, cause drug sensitization, relapse, bowel damage, disease-related complications and need for surgery.

A Cochrane review conducted by Boyapati et al evaluated the feasibility of discontinuing immunsuppressants and biologic agents, administered alone or in combination, in patients with quiescent CD.(40) A total of six RCTs (N = 326) satisfied the eligibility criteria and were meta-analyzed.

Four studies (215 participants) randomized patients in clinical remission to either continue or cease azathioprine monotherapy.(41-44) With respect to clinical relapse rates at 12 to 48 months, azathioprine cessation was significantly inferior to continuation. Thirty-two percent (36/111) of patients in the withdrawal group relapsed compared to 14% (14/104) of patients who continued receiving azathioprine (RR 0.42, 95% CI 0.24 to 0.72, p = 0.002). There were no between-group differences observed for development of new CD-related complications (RR 0.34, 95% CI 0.06 to 2.08, p = 0.24), adverse events (RR 0.88, 95% CI 0.67 to 1.17, p = 0.39), serious adverse events (RR 3.29, 95% CI 0.35 to 30.80, p = 0.30) or withdrawal due to adverse events (RR 2.59, 95% CI 0.35 to 19.04, p = 0.35). The quality of evidence for all outcomes was considered low due to potential for risk of bias and sparse data.

One blinded and one open-label RCT (111 participants) assessed azathioprine withdrawal from a therapeutic regime in which infliximab was concomitantly administered.(45, 46) Data pooling revealed similar relapse rates across groups: 48% (27/56) of patients who continued on azathioprine relapsed compared to 49% (27/55) of

patients who discontinued azathioprine (R 1.02, 95% CI 0.68 to 1.52, p = 0.32). The quality of evidence for this outcome was rated as low due to high risk of bias for blinding and sparse data. There were no statistically significant between-group differences in adverse event (RR 1.11, 95% CI 0.44 to 2.81, p = 0.83) or serious adverse event rates (RR 1.00, 95% CI 0.21 to 4.66). Evidence supporting these outcomes was considered low to very low due to high risk of bias for blinding and very sparse data.

The systematic review failed to identify any RCTs involving discontinuation of biologic therapy in patients with inactive CD.

Summary

At present, the effects of pharmacological withdrawal in patients with quiescent CD are uncertain. Continuous immunosuppressant monotherapy may be superior to cessation for avoiding clinical relapse. Conversely, there may be no substantial difference in clinical relapse rates when immunosuppressants are withdrawn from a combination therapy regime versus continued. It does not appear that stopping immunosuppressants, whether initially administered as monotherapy or combination therapy, significantly impacts the development of CD-related complications, adverse events, serious adverse events or withdrawal due to adverse events. These results should be interpreted with caution given that azathioprine is the only immunosuppressant that has been assessed in a randomized withdrawal trial and the very low to low quality of the supporting evidence.

Unfortunately, there are no controlled data on withdrawal of biologic agents in patients with inactive CD. However, a prospective cohort study (STORI) found that

approximately 44% of patients who achieved corticosteroid-free remission with concomitant infliximab and antimetabolite therapy relapsed within one year of infliximab cessation.(47) Predictive factors of relapse included male sex, absence of surgical resection and high leukocyte, hemoglobin, C-reactive protein and fecal calprotectin levels. These clinical and biochemical markers may be useful for identifying patients most likely to maintain remission. Observational data also suggests that therapeutic drug monitoring may provide valuable information on the best candidates for drug withdrawal.(48) Compared to blinded de-escalation, infliximab adjustment based on anti-drug antibody (ADA) and serum trough levels was associated with lower rates of relapse. Nevertheless, it is important to acknowledge that infliximab ADAs can be transient, and their presence does not necessarily lead to worse clinical outcomes.(49)

Cyclical treatment with immunosuppressants and biologic agents has been proposed as an alternative to de-escalation or permanent cessation.(50) No level-one evidence currently exists to support this paradigm, with critics citing the possibility of drug sensitization as a pitfall. While cyclical treatment with biologic agents may lead to short-term cost-savings, it is unclear whether this strategy will be cost-effective in the long term.

Efforts are underway to obtain controlled data on drug withdrawal in patients with quiescent CD. The BIOCYCLE project seeks to assess the efficacy, safety, effectiveness and feasibility of anti-TNFα and immunosuppressant withdrawal. As part of this initiative, the SPARE trial (A proSpective Randomized Controlled Trial comParing infliximAb-antimetabolites Combination Therapy to Anti-metabolites monotheRapy and Infliximab monothErapy in Crohn's Disease Patients in Sustained Steroid-free

Remission on Combination Therapy; NCT02177071) will randomize CD patients who have achieved sustained corticosteroid-free remission on concomitant infliximab and anti-metabolite therapy to continue combination therapy, cease infliximab or cease anti-metabolites. Outcomes of interest include clinical relapse rates, time in remission and the ability of biomarkers to predict relapse. This study is currently recruiting and expected to complete in late 2021.

STRATEGIES FOR DETECTING COLON CANCER IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

IBD patients are at increased risk for developing colorectal cancer (CRC), presumably because chronic inflammation gives rise to carcinogenesis, malignant transformation, tumor growth and metastasis.(51) In UC, the incidence rate of CRC ranges from 1.09 to 4.29 per 1000 person years disease duration (PYD), with older studies reporting higher estimates.(52) While CRC is less common in CD than UC (0.5 per 1000 PYD), the incidence of CRC is two to three times greater in patients with CD compared to the general population.(53, 54) In addition to causing psychological, social, and functional impairments, CRC accounts for approximately 15% of all IBD deaths.(55)

The Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease (SCENIC) international consensus statement – which is endorsed by the American Gastroenterology Association and American Society of Gastrointestinal Endoscopy – recommends chromoendoscopy with targeted biopsies for the identification of precancerous dysplasia.(56) Pooled

observational findings suggest that chromoendoscopy is more efficacious than standard-definition white-light endoscopy for dysplasia detection (RR 1.8, 95% CI 1.2 to 2.6) and controlled data indicate that chromoendoscopy is likely more sensitive than high-definition white-light endoscopy in patients with UC.(57) However, a recently published, multi-center, retrospective cohort study failed to demonstrate the superiority of chromoendoscopy over high-definition white-light endoscopy for detection of dysplastic lesions (10% versus 11% detection rate, respectively; p = 0.80).(58)

While dysplasia is an important surrogate of future colorectal cancer risk(59), its presence does not affect quality of life or mortality. Furthermore, enhanced dysplasia detection with chromoendoscopy does not necessarily translate into lower CRC rates. Resection of polypoid dysplasia appears to reduce the risk of CRC(60), yet it does not prevent non-polypoid or endoscopically invisible lesions from developing into high-grade dysplasia or cancer.(61) Unlike sporadic cancer, progression of IBD-associated cancer follows a molecular-genetic pathway in which clonal sweeps of aberrant crypts results in a genetically unstable mucosa.(62) Surgical removal of circumscribed dysplastic lesions does not mitigate the predisposition to cancer in UC and CD patients, and therefore may not reduce the likelihood of future CRC development in this population.

An updated Cochrane review by East et al aimed to assess the efficacy of cancer surveillance programs with respect to outcomes that are highly relevant to IBD patients.(63) Primary and secondary endpoints included the rate of CRC diagnosis, CRC-associated mortality, time to cancer detection, time to death and adverse events. Five relevant case-control studies (N = 7199) published between 1993 and 2014 were identified.(64-68)

The rate of CRC detection in IBD patients who underwent colonic surveillance versus non-surveillance was reported in three studies (7151 participants).(64, 66, 67) The between-group difference in CRC detection rates revealed a statistically significant difference in favor of surveillance (odds ratio [OR] 0.58, 95% CI 0.42 to 0.80, p <0.001). CRC was detected in 1.8% (53/2893) of patients who were screened and 3.2% (135/4256) of patients who were not screened.

Four studies assessed the CRC-associated death rate in IBD patients who participated in a surveillance program compared to those who did not (530 participants).(64, 65, 67, 68) The death rate was significantly lower in the surveillance group: 8% (15176) of these patients died from CRC compared to 22% (79/354) of patients who were not surveilled (OR 0.35, 95% CI 0.19 to 0.69, p = 0.002).

The rate of early-stage (Dukes stages A and B) and late-stage (Dukes stages C and D) CRC in IBD patients who underwent surveillance versus those who did not was reported in two studies (227 participants).(65, 67) The pooled analysis revealed that a significantly higher rate of early-stage CRC was detected in the surveillance group versus the non-surveillance group (16% [17/110] versus 8% [9/117], respectively; OR 5.40, 95% CI 1.51 to 19.30, p = 0.009). A significantly higher rate (16% [19/117]) of late-stage CRC was observed in the non-surveillance group relative to the surveillance group (9% [10/110]; OR 0.46, 95% CI 0.08 to 2.51; p = 0.37).

The quality of evidence for all outcomes reported in this systematic review were rated as very low due to the possibility of risk of bias introduced by the observational

design of the meta-analyzed studies and sparse data. Time to cancer detection, time to death and adverse event data were not available.

Summary

Colonoscopic screening programs may both curb CRC development and the number of CRC-associated deaths in IBD patients through early detection. However, other factors may have contributed to reduced CRC morbidity and mortality rates, including the introduction of novel biologic agents, top-down therapy and mucosal healing as a treatment goal. While results from RCTs could eliminate potential confounders, this study design is unlikely to be implemented within the context of endoscopic surveillance due to ethical concerns. Evidence from retrospective case control studies in this area is increasingly difficult to obtain, since the majority of IBD patients undergo surveillance in the modern era. Although chromoendoscopy improves dysplasia detection in IBD (56), it remains unclear whether this impacts the development of CRC or death associated with CRC beyond high definition white light examination. If chromoendoscopy is used it should be focused on those at highest risk e.g. patients with previous dysplasia, PSC, longstanding extensive disease, and performed by those with expertise and training in the technique.

Further research is needed to provide insight into whether chromoendoscopy is superior to high-definition white-light surveillance given the current conflicting evidence base. It would also be prudent for future studies to focus on evaluating the relative merits of risk-stratified versus fixed surveillance strategies. Finally, there is a need for

non-invasive tests, such as fecal DNA or rectal mucosal FISH analysis, capable of accurately identifying IBD patients at high risk for developing CRC.

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