Received: 23 March 2020 | First decision: 3 April 2020 | Accepted: 15 April 2020

DOI: 10.1111/apt.15771

AP&T Alimentary Pharmacology & Therapeutics WILEY

Review article: withdrawal of 5-aminosalicylates in inflammatory bowel disease

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Summary

Background: 5-aminosalicylates (5-ASA) are widely used in inflammatory bowel disease (IBD), but emerging evidence suggests that they may be safely withdrawn in significant subsets of patients. This is important to address: 5-ASA therapy accounts for up to 25% of total healthcare costs in ulcerative colitis (UC), while almost a third of patients with Crohn's disease (CD) receive long-term 5-ASA despite no clear evidence of benefit. Further, rationalising medication burden may improve overall adherence and outcome.

Aims: To summarise the rationale for 5-ASA withdrawal, review the current evidence in both UC and CD and consider the data surrounding colorectal cancer (CRC) prevention, guiding an evidence-based withdrawal strategy.

Methods: PubMed was searched to identify relevant studies. Only papers published in English were reviewed, with priority given to randomised clinical trials and meta-analyses.

Results: For patients with UC, consideration of 5-ASA withdrawal should be made on a case-by-case basis, but it appears safest for those in deep remission without any of the following risk factors: younger age (<40 years), remission for less than 2 years, a history of multiple flares, extensive disease. 5-ASA withdrawal should also be considered in patients with UC escalated to biologic therapy who have achieved remission and in all patients with CD. Although 5-ASA therapy may have chemopreventive benefits for CRC, the cost-benefit ratio appears significant, and this indication is not justified by evidence in those who have achieved remission and are continuing therapy with other agents, or in those in sustained remission without a history of extensive disease.

Conclusions: Although the majority of patients with IBD receive 5-ASA during their disease course, safe withdrawal appears possible in many, with important implications for both health economics and patient experience. A number of unanswered questions, however, remain.

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The Handling Editor for this article was Professor Jonathan Rhodes, and this commissioned review was accepted for publication after external peer review.

1 | INTRODUCTION

5-aminosalicylates (5-ASA) are the mainstay of treatment for mild-to-moderate ulcerative colitis (UC) and are widely prescribed.[1,2] Indeed, 88%-97% of patients receive 5-ASA therapy within a year of first diagnosis, with 60%-87% continuing at 10 years.[3] However, despite the increasing therapeutic armamentarium available, it is apparent from clinical trial data that clinicians persist with 5-ASA therapy even when it has demonstrably failed and treatment escalation is undertaken. In the ACT1 and 2 studies of infliximab in moderate-to-severe UC, approximately 70% of patients received concurrent 5-ASA,[4] with the PURSUIT studies of golimumab a decade later showing prescribing habits remained unchanged.[5] Furthermore, over half of patients with Crohn's disease (CD) receive 5-ASA during their disease course, with up to 30% continuing long term, despite no convincing evidence of benefit and both European and US guidelines advising against their use.[6-10]

At a time of increasing pressure on healthcare budgets worldwide, recent guidelines have emphasised the importance of addressing low-value healthcare.[11,12] The true cost of 5-ASA therapy is often underappreciated by clinicians, with a study in the United Kingdom suggesting it accounted for up to 25% of total healthcare costs in UC, with an average annual maintenance prescription estimated to be £740/€850.[13,14] There is little evidence that 5-ASA expenditure is reducing, although a very recent study has suggested that the increasing use of biologic therapy has reduced the relative contribution of 5-ASA to total healthcare costs in UC.[15] However, it is notable that the cost differential with some biologics has now begun to narrow significantly with the advent of anti-tumour necrosis factor (TNF) biosimilars.

While rightly considered to be a safe and well-tolerated therapeutic class, 5-ASA have been associated with rare but serious idiosyncratic adverse effects including pancreatitis, although a recent study has cast doubt on the association with nephrotoxicity,[16] while around 3% of patients report a paradoxical worsening of diarrhoea.[17] Of more significant concern is the observation that use of 5-ASA in CD may delay the introduction of effective therapy, potentially impairing clinical outcomes. The negative impact of polypharmacy must also be considered, with non-adherence linked to higher daily pill burden.[18] Indeed, the additional burden of an inconvenient and more complex medication regimen has been linked to poorer outcomes in both UC and a variety of other conditions, with real-world compliance as low as 50%.[19] Furthermore, topical 5-ASA therapy is frequently poorly tolerated by patients, and adherence is significantly worse than oral therapy.[20]

There is thus a clear need to consider the issue of withdrawal of 5-ASA therapy in IBD, with emerging evidence suggesting it may be safely stopped in significant subsets of patients. In this review, we comprehensively discuss the data surrounding 5-ASA withdrawal in both UC and CD, including the role of 5-ASA in colorectal cancer (CRC) chemoprevention. We review the advice from recent drug withdrawal guidelines and propose a withdrawal strategy before concluding with future perspectives.

1.1 | Search strategy

An electronic search of Pubmed was conducted to identify relevant manuscripts from their inception until February 2020. The search combined the MeSH terms "inflammatory bowel disease", "Ulcerative Colitis" and "Crohn's Disease" with the subheadings "5-ASA withdrawal", "5-ASA de-escalation", "risk of relapse", "cost saving" and "colorectal cancer". We also reviewed bibliographies of the included studies to identify additional important data. Recent guidelines and topical reviews were also assessed. Only papers published in English were reviewed, with priority given to randomised clinical trials (RCT) and meta-analyses.

2 | 5-ASA WITHDRAWAL IN UC

2.1 | Withdrawal of topical 5-ASA monotherapy in distal colitis

Six randomised clinical trials have evaluated topical 5-ASA withdrawal in patients with distal UC (Table 1).[21-26] All RCTs assessed mesalazine (mesalamine)-based treatment, but the frequency and mode of administration varied between the studies. The longest follow-up period was 2 years post-withdrawal.[23] All 6 RCTs reported higher relapse rates in the placebo group compared to the 5-ASA treatment group. Relapse rates in the placebo group ranged from 52% to 85% at 12 months up to 91% at 24 months, whereas relapse rates in patients who continued 5-ASA ranged from 20% to 48% at 12 months up to 55% at 24 months. In summary, stopping topical therapy in distal UC is associated with significantly higher rates of disease relapse. No studies were identified that assessed dose de-escalation, although reduction in frequency of administration is commonly used in clinical practice once remission has been achieved. Furthermore, 1 g of mesalazine once daily appears to be the optimal dose for induction of remission, suggesting no benefit to more frequent dosing strategies in maintenance of remission.[27]

2.2 | Withdrawal of oral 5-ASA monotherapy

In total, five RCTs were identified that assessed withdrawal of oral 5-ASA therapy in UC (Table 2).[28-32] A total of 515 patients were analysed during 6-12 months of follow-up. Although the 5-ASA preparation and frequency varied, with sulfasalazine, olsalazine and mesalazine all assessed, most RCTs[28-30,32] found a higher rate of relapse in patients who stopped oral 5-ASA compared to those who continued therapy. Relapse rates in the placebo group ranged from 29% to 60.3% at 6 months and 26% to 49% at 12 months, whereas relapse rates in patients who continued 5-ASA ranged from 12.1% to 41.2% at 6 months and from 18% to 23% at 12 months. Only a single RCT found no significant difference in relapse rate but relapse was defined solely with clinical symptoms leading to risk of bias.[31] Results from retrospective studies are in agreement with the overall RCT

TABLE 1 Randomised clinical trials comparing the rate of relapse after topical 5-ASA withdrawal

	Participants and follow-up duration	Type of therapy	Disease extent	Definition of relapse	Treatment group	Relapse rate
Biddle et al[26]	25 12 mo	Mesalazine enema 1g od	100% left-sided colitis	Endoscopic: "Erythematous, oedematous and friable mucosa" at sigmoidoscopy	Mesalazine group: 12 Placebo group: 13	Mesalazine group: 25% Placebo group: 84.6%
D' Arienzo et al[22]	30 12 mo	Mesalazine suppositories 400 mg bd	43% proctosigmoiditis 57% proctitis	Endoscopic: Blackstone's modified endoscopic score > 1 at sigmoidoscopy	Mesalazine group: 12 patients (2 left the study) Placebo group: 14 patients (1 left the study)	Mesalazine group: 8.3% (1/12) Placebo group: 78.6%
Miner et al[21]	157 6 mo	Mesalazine enema 4 g od, 4 g every other day or 4 g every 3 days	100% left-sided colitis	Clinical and endoscopic: Rectal bleeding or increased stool frequency for ≥ 3 successive days and active inflammation at endoscopy or moderate mucosal inflammation alone at endoscopy	Mesalazine group: 113 Placebo group: 44	Mesalazine group: 27.4% Placebo group: 52.3%
D'Albasio et al[25]	111 12 mo	Mesalazine 500 mg bid or Mesalazine 500 mg od (40 patients)	100% proctitis	Clinical and endoscopic: Development of symptoms and a Baron score of > 1 at sigmoidoscopy	Mesalazine 500 mg bid (36 patients) Mesalazine 500 mg od (40 patients) Placebo (35 patients)	Mesalazine bid: 10% Mesalazine od: 32% Placebo: 47%
Marteau et al[24]	95 12 mo	Mesalazine suppositories 1 g three times in a week	100% proctitis	Clinical and endoscopic: Clinical symptoms and an increase in the endoscopy score > 1	Mesalazine group: 48 Placebo group: 47	Mesalazine group: 47.9% Placebo group: 61.7%
Hanauer et al[23]	65 24 mo	Mesalazine 500 mg od	100% proctitis	Clinical and endoscopic: Rectal bleeding or increase in stool frequency for ≥ 1 wk and evidence of endoscopic inflammation	Mesalazine group: 31 Placebo group: 34	Mesalazine group: 46% Placebo group: 89%

Abbreviations: Bd, twice daily; Od, once daily; Qds, four times daily; Tds: tree times daily.

TABLE 2 Randomised clinical trials comparing the rate of relapse after oral 5-ASA withdrawal

	Participants and follow-up duration	Type of therapy	Disease extent	Duration of 5-ASA prior to randomisation	Definition of relapse	Treatment group	Relapse rate	Notes
Dissanayake and Truelove[32]	64 6 mo	Sulfasalazine 500 mg qds	Not reported	≥1 yr	Endoscopic: Active inflammation on sigmoidoscopy	Sulfasalazine group: 33 Placebo group: 31	Sulfasalazine group: 12.1% Placebo group: 54.8%	Results were similar whether the patients had received maintenance therapy for shorter (<3 yr) or longer (>3 yr) duration
Riis et al[31]	49 6 mos	Sulfasalazine at dose previously taking	Not reported	≥1 yr	Clinical: Rectal bleeding for > 3 successive days or > 3 stools per day for > 5 d	Sulfasalazine group: Placebo group:	Sulfasalazine group: 24% Placebo group: 29%	Inclusion was based on symptoms; endoscopy findings were not considered
Sandberg-Gertzen et al[30]	102 6 mo	Olsalazine 500 mg bd	41% pancolitis 51% left-sided colitis 8% proctitis	≥6 mo	Clinical and endoscopic: Bloody diarrhoea and active inflammation at sigmoidoscopy	Olsalazine group: 52 Placebo group: 49	Olsalazine group: 23.1% Placebo group: 44.9%	
The Mesalazine study group (MSG)[29]	189 (initially 264 were randomised but 189 were compliant with the protocol) 6 mo	Mesalazine (Asacol) 400 mg bd or qds	28% pancolitis 18% left-sided colitis 39% proctosigmoiditis	≥1 mo	Endoscopic: Endoscopic relapse	Mesalazine 400 mg bd group: 68 Mesalazine 400 mg qds group: 58 Placebo group: 63	Mesalazine 400 mg bd group: 41.2% Mesalazine 400 mg qds group: 34.5% Placebo group: 60.3%	
Ardizzone et al[28]	112 12 mo	Mesalazine (Asacol) 400 mg tds	20% pancolitis 35% left-sided colitis 45% proctosigmoiditis	≥1 yr	Clinical and endoscopic: Increased stool frequency with blood or mucus and evidence of active inflammation on sigmoidoscopy	Group A Mesalazine: 26 Placebo: 35 Group B Mesalazine: 28 Placebo: 23	Group A Mesalazine: 23% Placebo: 49% Group B Mesalazine: 18% Placebo: 26%	Group A: remission for 1-2 yr Group B: remission for >2 yr (median 4 yr). Nonsignificant difference was observed in group B

Abbreviations: Bd, twice daily; Od, once daily; Qds, four times daily.

findings, with relapse rates higher than 50% in patients who stopped 5-ASA reported.[33] Importantly, Ardizzone et al compared 12-month relapse rates with duration of remission before therapy withdrawal.[28] Patients who had been in remission for more than 2 years before withdrawal of 5-ASA did not have a significantly higher relapse rate than those who continued (26% vs 18%, $P = 0.35$). In comparison, patients who had been in remission for 1-2 years before withdrawal of 5-ASA did have a significantly higher relapse rate than those who continued (49% vs 23%, $P = 0.035$). The authors concluded that continuation of 5-ASA treatment is necessary for patients who have been in remission for less than 2 years. In summary, withdrawal of oral 5-ASA when used as monotherapy is associated with a higher relapse rate. However, the majority of studies included patients who had been in remission for less than 12 months before withdrawal, and thus further studies assessing the safety of withdrawal in patients in long-term remission are warranted.

2.3 | Dose de-escalation of 5-ASA therapy

Although the risk of relapse on withdrawal of 5-ASA monotherapy appears high, an alternative approach is dose reduction, which may still yield important cost savings and reduce pill burden. European Crohn's and Colitis Organisation (ECCO) guidelines on the management of UC suggest that 2 g daily of oral 5-ASA is effective in maintaining remission, while for distal disease topical treatment with 3 g/week in divided doses may be sufficient.[1] A retrospective national database study of 4452 patients found no significant difference in risk of flares between patients treated with low- (2.2-2.8 g/day) vs high-dose (4.4-4.8 g/day) mesalazine, during a median of follow-up of 6 years.[34] However, patients with low adherence had a lower risk of relapse with high-dose 5-ASA (hazard ratio [HR] 0.28, $P = 0.003$).[34] As expected, one RCT found that a dose of just 1.2 g/day oral mesalazine was less effective than 2.4 g/day in maintaining remission, particularly in those patients with a history of more frequent relapses.[35] A further RCT found that 4.8 g/day oral mesalazine was superior to 2.4 g/day in maintaining remission in patients under the age of 40 and/or with extensive disease.[36] In summary, it appears safe to dose de-escalate in selected patients, but those younger than 40 years, or who have poor adherence or extensive colitis may require continuation of high-dose 5-ASA.

2.4 | Withdrawal of topical and/ or oral 5-ASA when used in combination

Three studies have evaluated topical 5-ASA withdrawal in patients treated with concomitant oral therapy. D'Albasio et al randomised patients either to receive combined therapy with oral 5-ASA 4.6 g/day and 5-ASA enemas 4 g twice weekly or oral 5-ASA with placebo enemas over 12 months. Relapse rates were higher in patients where topical 5-ASA therapy was withdrawn in comparison to those where both oral and topical 5-ASA therapy was continued (23/36 patients 69% vs 13/33 39%, $P = 0.036$).[37] Similarly, Yokoyama et al randomised patients either to receive oral 5-ASA (3 g/day) with 5-ASA enema 1g twice weekly or oral 5-ASA alone. The enemas were only administered at weekends, with the hypothesis that they would be better tolerated by patients who worked or attended school. Relapse rates were again higher in patients where topical 5-ASA therapy was withdrawn (10/13 patients 76.9% vs 2/11 18.2%).[38] Piodi et al compared combined therapy with oral 5-ASA (1.6 g/day) and 5-ASA enemas (2 g twice weekly) with oral 5-ASA monotherapy. Patients on combined therapy had lower mean relapse rate (1.59 vs 2.76, $P = 0.034$) and higher probability of not having a first relapse during the observation period (0.59 vs 0.29, $P = 0.001$).[39] In summary, continuation of topical therapy is associated with higher rates of remission in patients with concomitant oral 5-ASA therapy, although the study by Yokoyama et al suggested that it may be possible to de-escalate the frequency of topical therapy, given the promising results from a weekend enema alone.[38] Importantly, all studies included patients who had been in remission for only a month prior to de-escalation, and thus the outcome in patients in long-term remission requires further investigation.

2.5 | Withdrawal of 5-ASA in patients treated with immunomodulators

Two studies have evaluated the outcome of oral 5-ASA withdrawal in patients treated with concomitant immunomodulators. Mantzaris et al randomised 70 steroid-dependent patients with UC to receive azathioprine (AZA) monotherapy (34/70) or in combination with olsalazine (36/70) for 2 years with no difference in relapse rates reported (26.2% vs 25%, P = NS). However, treatment compliance was significantly better for the AZA monotherapy group (97% vs 85%, $P < 0.001$).[40] In a retrospective study of patients with IBD in clinical remission for a minimum of 6 months that included 82 patients with UC, no difference in relapse rate was found between patients with UC receiving either AZA monotherapy or combination AZA and oral 5-ASA therapy (0.19 relapse per year of follow-up vs 0.21/year of follow-up, $P = 0.69$), during a 4.3-year follow-up period.[41] Importantly, both studies only assessed clinical relapse, with no biochemical or endoscopic evaluation included, and thus the overall level of evidence must be considered weak.[40] Therefore, further prospective studies are warranted to clarify if 5-ASA therapy can be safely withdrawn in patients on AZA. Interestingly, it has been suggested that 5-ASA therapy may potentiate thiopurine efficacy, with studies demonstrating that mesalazine increases levels of the active thiopurine metabolite 6-thioguanine, although the mechanism for this remains unclear.[42,43]

2.6 | Withdrawal of 5-ASA in patients treated with biologic therapy or tofacitinib

No RCTs have yet evaluated the outcome of 5-ASA withdrawal in patients treated with biologic therapy. However, a recent retrospective

cohort study provides important data.[44] A total of 3589 patients with moderate-to-severe UC from two national population-based databases (USA and Denmark) were included to compare adverse clinical events in patients who discontinued oral 5-ASA within 90 days of initiation of anti-TNF therapy with those who continued 5-ASA. Stopping 5-ASA did not increase the risk of adverse clinical events, including corticosteroid use (2.7% vs 4.3%, $P = 0.10$), hospitalisation (5.2% vs 6.2%, $P = 0.70$) and surgery (6.7% vs 7.7%, $P = 0.46$). Overall, stopping 5-ASA did not increase the risk of adverse clinical events in either the US cohort (aHR 1.04, 95% CI 0.88-1.23, $P = 0.67$) or the Danish cohort (adjusted hazard ratio [aHR] 1.09, 95% CI 0.80-1.49, $P = 0.6$). Results were similar in sensitivity analyses assessing concomitant immunomodulator therapy and duration of 5-ASA treatment.

Separately, a post hoc analysis of clinical trials assessed the outcome of concomitant 5-ASA in patients escalated to anti-TNF therapy, although the issue of 5-ASA withdrawal was not specifically addressed.[45] An individual participant data analysis of 2183 patients pooled from 5 clinical trials of infliximab and golimumab in moderate-to-severe UC were undertaken. Maintenance of 5-ASA oral therapy was not associated with increased odds of clinical remission (adjusted odds ratio [aOR] 0.67, $P = 0.06$), clinical response (aOR 0.89, $P = 0.58$), biochemical response (aOR 0.94, $P = 0.79$) or mucosal healing (aOR 1.12, $P = 0.48$). However, the impact on two important long-term outcomes, surgery and risk of CRC, was not assessed.

A further recent retrospective cohort study has assessed concomitant 5-ASA therapy in patients treated with the anti-integrin therapy vedolizumab.[46] There was no difference in steroid-free clinical remission (56.8% vs 66%, $P = 0.36$) or endoscopic remission (42.5% vs 53.1%, $P = 0.32$) in patients treated with or without aminosalicylates, in a 12-month period of follow-up. These data are further supported by results from a *post hoc* analysis of the GEMINI long-term safety study, with no difference found in survival probabilities for vedolizumab treatment persistence at 54 months, between patients who initiated vedolizumab with or without concomitant medications, including 5-ASA.[47]

No prospective studies or RCTs have evaluated the outcome of 5-ASA withdrawal in patients treated with the Janus kinase (JAK) inhibitor tofacitinib. Indirect evidence from subgroup analysis of RCTs suggests concomitant 5-ASA at trial entry does not affect likelihood of maintaining clinical remission after escalation to tofacitinib or anti-TNF therapy (relative risk [RR] 0.92, 95% CI 0.78-1.09).[48]

In summary, concomitant 5-ASA therapy in patients escalated either to anti-TNF or vedolizumab does not appear to improve UC-related outcomes and withdrawal may therefore be considered. However, data from randomised controlled trials, where withdrawal of 5-ASA therapy is directly compared to continuation in patients escalated to advanced therapy, are required to confirm these findings.

2.7 | Predictive factors for relapse on withdrawal of 5-ASA in UC

Few studies have identified clear predictive factors for relapse after 5-ASA withdrawal. As discussed above, it appears that patients younger than 40 years and/or with more extensive disease are at higher risk of relapse on dose de-escalation.[34,35] Both of these factors have been associated with a more active disease course, which itself is very likely to predict a higher risk of relapse on 5-ASA withdrawal.

Increasing interest has focussed on whether the attainment of deep remission, defined as clinical, biochemical and endoscopic remission, is associated with reduced risk of relapse. However, to date only histological grade has been clearly associated with risk of relapse in patients with UC.[49] In a prospective study of 179 patients, the relative risk of clinical relapse was 3.5 (95% CI 1.9-6.4, $P < 0.0001$) in patients where baseline Geboes grade was >3.1 following multivariate analysis. In contrast, baseline Mayo endoscopy score (MES) was associated with risk of relapse on univariate but not multivariate analysis. However, a retrospective study has suggested that remission is more likely to be maintained following 5-ASA dose de-escalation if MES is 0.[50]

Recently it has been shown that faecal calprotectin (FC) may be used as a non-invasive surrogate measure of histological remission. A review of 12 studies, involving 1168 patients, found that FC positively correlated with histologic disease activity in all studies. However, no single cut-off value could be obtained to accurately predict histologic remission, with values ranging from 40.5 to 250 μg/g, as the cut-off level varied between studies and test used, and according to the definition of histological remission.[51] Although no study has specifically assessed the use of FC to guide 5-ASA withdrawal in UC, two prospective studies have suggested that patients in clinical remission on oral 5-ASA with FC levels >200 and 300 μg/g, respectively, were at higher risk of relapse.[52,53]

2.8 | Monitoring and treatment of relapse

It is clear that patients and clinicians alike may underestimate the relevance of mild symptoms,[54] and thus it is essential that patients are objectively monitored for evidence of disease relapse if 5-ASA is withdrawn. FC has recently emerged as a potentially useful objective predictor of early relapse before clinical recurrence. One prospective study has suggested that higher FC predicts short-term risk of relapse in patients in deep remission following anti-TNF withdrawal, with FC levels elevated up to 6 months before evidence of endoscopic activity.[55]

No studies have yet directly addressed the efficacy of re-treatment with 5-ASA in the event of relapse. Two studies have, however, suggested that dose escalation of 5-ASA in patients in clinical remission with elevated FC lowers relapse rate, suggesting that FC monitoring might allow early reintroduction or dose escalation of 5-ASA before clinical recurrence.[42,43]

3 | 5-ASA WITHDRAWAL IN CD

3.1 | Withdrawal of 5-ASA monotherapy

Despite ongoing widespread use of 5-ASA monotherapy in CD, most commonly in elderly patients or those with mild disease,[8,9] there are

little data on outcomes following withdrawal. It is, however, clear that 5-ASA are ineffective in maintaining remission, with a Cochrane meta-analysis of 2014 patients from 11 studies reporting no difference in relapse rate at 1 year follow-up between patients treated with 5-ASA and placebo (53% (526/998) vs 54% (544/1016), RR 0.98, 95% CI 0.91-1.07, P = 0.70).[56] The overall data, although only of moderate quality, were considered sufficient for the authors to recommend that additional randomised trials may not be justified. However, a retrospective Danish study of 537 patients with CD treated with first-line mesalazine monotherapy had previously raised the concept of 5-ASA dependency.[57] This phenomenon, defined as clinical relapse within 1 year of stopping mesalazine with a regain of response after restarting mesalazine, was observed in 23%. These results should, however, be interpreted with caution as they are at risk of significant bias, including a failure to consider factors known to influence disease course such as smoking status. Furthermore, the apparent symptomatic benefit may simply be explained by a placebo effect, which is well documented in CD.[58]

Separate research has focussed on the potential role of 5-ASA to prevent relapse following surgery for CD. A Cochrane meta-analysis of 730 patients from 5 RCTs reported a lower rate of clinical relapse in patients treated with 5-ASA vs placebo (36% (131/361) vs 43% (160/369) (RR 0.83, 95% CI 0.72-0.96)), during a follow-up that ranged from 48 to 72 weeks.[59] No conclusion could, however, be made based on endoscopic or radiological evidence of relapse due to insufficient data. Again, without clear objective evidence of benefit, these results should therefore be interpreted with caution, and once again the apparent symptomatic benefit may be explained by a placebo effect.

3.2 | Withdrawal of 5-ASA in patients treated with immunomodulators

A retrospective study by Campbell et al that included 104 patients with CD on azathioprine found no difference in relapse rate between those on combination therapy and those on azathioprine alone (mean relapse rate 0.27/year vs 0.30/year, P = ns).[41] No studies have reported withdrawal of 5-ASA therapy from patients on combination therapy with methotrexate.

3.3 | Withdrawal of 5-ASA in patients treated with biologic therapy

A recent large retrospective database analysis of 3178 patients with CD, comprising independent cohorts from the United States (2960 patients) and Denmark (218 patients), explored the effects of discontinuing mesalazine therapy when initiating anti-TNF. No increased risk of adverse clinical events (corticosteroid use, hospitalisation or surgery) on withdrawal of mesalazine was found following multivariable Cox regression modelling in either the US cohort (aHR 0.89, 95% CI 0.77-1.03, P = 0.13) or the Danish cohort (aHR 1.13, 95% CI 0.68-1.87, P = 0.63).[44] Furthermore, and in agreement with the study by Campbell et al, the concurrent use of immunomodulators had no apparent effect on the risk of adverse outcomes following mesalazine withdrawal.[41] No studies have yet assessed 5-ASA withdrawal in patients treated with vedolizumab or the anti-IL12/23 biologic ustekinumab in CD, but there is no reason to suspect an increased risk of adverse events.

4 | THE ROLE OF 5-ASA IN CRC PREVENTION—A KEY CONSIDERATION?

The development of CRC in patients with inflammatory bowel disease is a significant concern for both clinicians and patients, with a meta-analysis of 116 studies from across the world reporting an incidence of 0.3% per year in UC,[60] and a separate meta-analysis suggesting a comparable risk in Crohn's colitis.[61] A very recent population-based cohort study from Scandinavia has suggested that the risk of CRC for patients with UC has decreased over the last five decades, with an overall HR of 1.66 (95% CI 1.57-1.76) compared to the general population.[61] In a separate population-based cohort study, the same authors reported a HR of 1.74 (95% CI 1.54-1.96) for patents with CD compared to the general population.[63]

The potential role of 5-ASA in CRC prevention is consequently of great interest. It is clear that CRC risk depends on inflammation dependent factors, namely duration, extent and severity of colonic disease and inflammation independent factors, predominantly family history and presence of primary sclerosing cholangitis (PSC).[64] The first benefit of 5-ASA appears to relate to control of colonic inflammation, and therefore as expected is not specific to 5-ASA. A recent systematic review and meta-analysis of 27 studies involving 95 937 patients with IBD demonstrated that thiopurine use was associated with a reduced risk of both high-grade dysplasia and CRC, particularly among those with a longer disease duration,[65] although the risk reduction appeared limited to those with UC in a separate meta-analysis.[66] The second potential benefit relates to the postulated direct chemopreventive effects of 5-ASA, with studies suggesting a range of relevant biological mechanisms including cell checkpoint activation,[67] improvement of DNA replication fidelity,[68] scavenging of reactive oxygen and nitrogen species[69] and interference with Wnt/beta-catenin signalling.[70] A recent observational study evaluated transcript levels of carcinogenesis-associated known 5-ASA target genes in colonic mucosa from patients with UC receiving long-term 5-ASA therapy. Significant suppression of the expression of a number of carcinogenesis-associated genes was reported in serial colonic biopsy specimens, with some transcript level changes independent of parameters of disease severity.[71] These apparent direct chemopreventive effects are noteworthy and may provide a rationale for long-term 5-ASA use.

A meta-analysis of 31 observational studies including 2137 cases of colorectal neoplasia, of which 76% were cancer, found that 5-ASA at therapeutic dose was associated with a significant reduction in neoplasia in UC (RR 0.54, 95% CI 0.38-0.64) but not CD (RR 0.76, 95% CI 0.43-1.33), with no benefit seen with sulfasalazine.[72] It is notable, however,

that not all studies have reported a protective effect, including a population-based study from Canada,[73] and indeed the overall effect appears consistently weaker in population-based studies.[72] The cost-benefit ratio of 5-ASA in chemoprevention has been estimated at 153 × annual cost of therapy per CRC prevented, which would be equivalent to around £110 000/€130 000.[64] This estimate may, however, significantly overestimate the cost benefit particularly if, as seems almost certain, the protective effect of 5-ASA is partly due to improved disease control. This represents a considerable expenditure, which might conceivably be spent more effectively on other strategies to prevent CRC including improved disease control and endoscopic surveillance.

British Society of Gastroenterology (BSG) guidelines state that patients with UC or IBD-U (IBD unclassified) with left-sided or more extensive disease should be advised to take at least 2 g mesalazine daily to reduce risk of CRC.[2] ECCO guidance is that the lifelong chemoprevention with 5-ASA is justified in all patients with UC, except for those with isolated proctitis.[74] While the most recent guidelines from the American Gastroenterological Association advise that 5-ASA may be withdrawn in all who have achieved remission with immunomodulator, biologic agents or tofacitinib, this recommendation did not factor in the potential chemopreventive benefit of 5-ASA.[48] However, the AGA guidelines do note that sustained remission appears protective regardless of the type of therapy used.

5 | STATE OF ART

5.1 | Current recommendations for the withdrawal of 5-ASA therapy in IBD

In 2018, ECCO published guidance on treatment withdrawal in IBD, including 5-ASA. In general, it was suggested that 5-ASA treatments should not be discontinued in patients with UC, even during remission, considering their benefits for both disease control and prevention of CRC. However, the importance of individualising any withdrawal decision is emphasised, and it was suggested that treatment withdrawal might be considered in patients with limited disease extent, a history of remission for several years, a history of a single disease flare only and no previous requirement for systemic corticosteroid therapy.[75] However, this guidance predates the recent publications suggesting no benefit to concomitant 5-ASA in patients escalated to anti-TNF or vedolizumab.[44,46] As noted above, in the recent AGA guidelines on management of moderate-to-severe UC, it has been suggested that 5-ASA therapy may be stopped in patients who have achieved remission with biologic agents and/or immunomodulators, or tofacitinib.[48] Neither European nor US guidelines recommend the use of 5-ASA therapy in CD.[6,7]

5.2 | A proposed withdrawal strategy

While we accept that some of the data described in this review are derived from studies that did not directly address the question of 5-ASA withdrawal, and there are still important gaps in our knowledge, we believe there is now sufficient evidence to guide decision making on 5-ASA withdrawal in significant subsets of patients. We propose that 5-ASA withdrawal should be considered in all patients with CD, but only following careful discussion with the patient, as they may be reluctant to consider this. A pro-active strategy of objective monitoring for evidence of relapse, including use of FC, may provide reassurance for both clinician and patient following withdrawal. For patients with PSC and IBD, who are at highest risk of CRC, it may be appropriate to continue 5-ASA for the additional chemopreventive benefits, although a low level of evidence supports this.

For patients with UC, consideration of 5-ASA withdrawal should be made on a case by case basis in collaboration with the patient, with decision making based on the presence or absence of key risk factors. For patients on high-dose 5-ASA dose de-escalation rather than complete withdrawal may still yield important benefits. A potential algorithm is outlined in Figure 1.

As with CD, patients with UC may develop a psychological dependency upon 5-ASA, with a perception that it continues to provide substantial benefit from previously distressing symptoms, and careful discussion may therefore be required. Although recent data suggest no benefit to continuing 5-ASA in patients escalated to biologic therapy, these studies were underpowered to assess the potential chemopreventive benefits of 5-ASA.[46,76] While we await further studies to help address the relative contributions of different UC medications to CRC prevention, it may be safest to continue 5-ASA until remission has been achieved with biologic therapy, although patients can be de-escalated from high-dose 5-ASA. As it currently remains difficult to accurately predict who may relapse, patients should be reassured that they will be closely monitored following de-escalation, allowing early detection of disease recurrence. The cost and potential inconvenience of this monitoring may, however, be significant and should be considered when weighing up 5-ASA withdrawal, although a FC test costs considerably less than 1 month of oral 5-ASA therapy.[13] The current life circumstances should also be considered; for example, one might decide not to de-escalate prior to a period of travelling where monitoring might be difficult, or prior to events such as university examinations where a flare may be more challenging.

6 | FUTURE PERSPECTIVES

Despite the convincing evidence to date and clear advice from national guidelines, clinicians continue to prescribe 5-ASA in CD. The ongoing STATIC study (Stopping Aminosalicylate Therapy in Inactive Crohn's Disease, NCT03261206), where patients with CD in clinical remission are randomised either to continue or stop 5-ASA therapy, with the primary outcome CD-related complications at 24 months will provide important prospective data with the hope it will finally change practice. Furthermore, increasing awareness of the need to target low-value healthcare, and the future emergence of effective and safe, well-tolerated treatments appropriate for mild colonic CD, or indeed the acceptance that no treatment may be an acceptable approach, may also change prescribing habits.

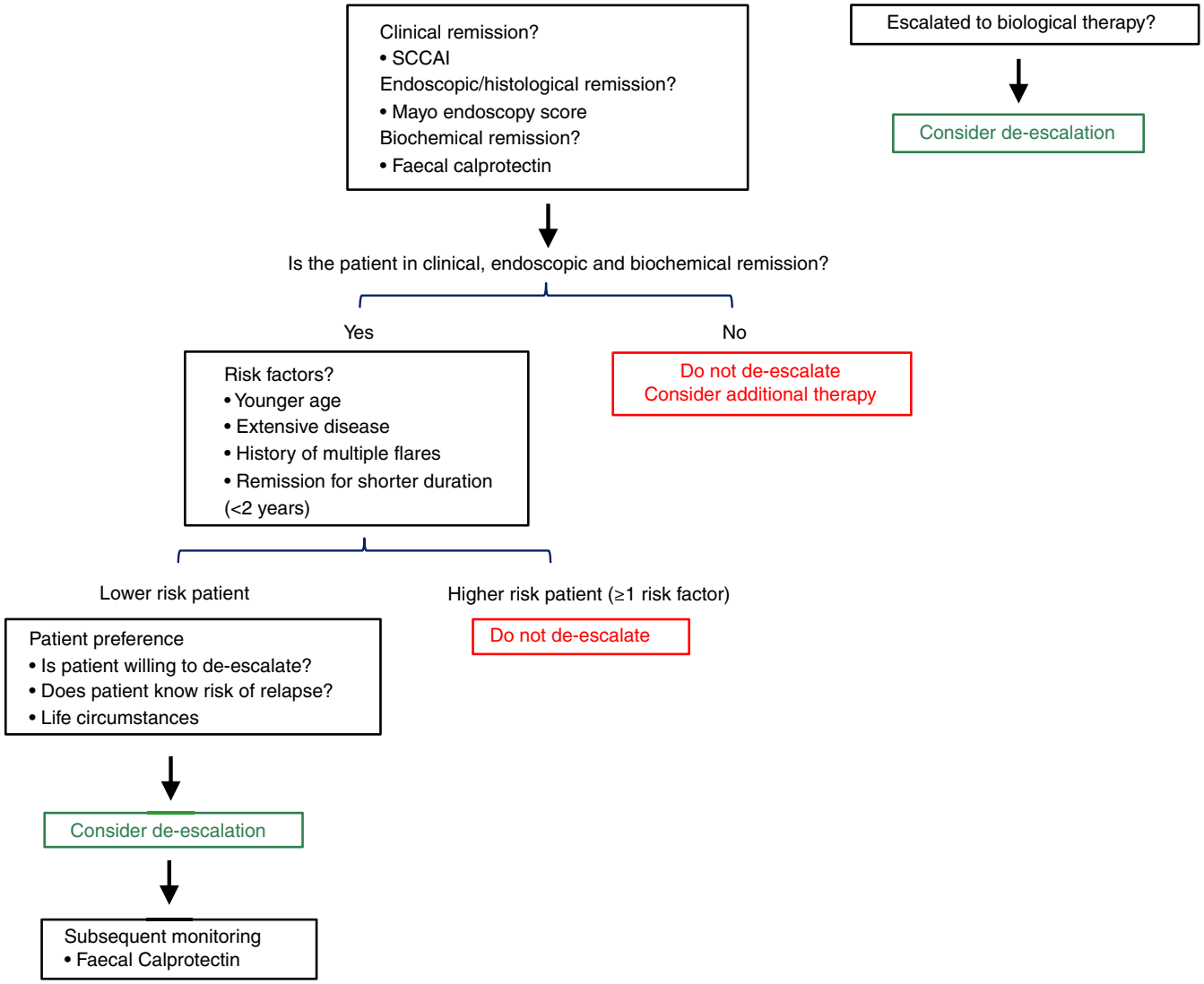

FIGURE 1 A strategy for 5-ASA de-escalation in ulcerative colitis. For patients with primary sclerosing cholangitis, it may be appropriate to continue 5-ASA in all cases. SCCAI, simple clinical colitis activity index

TABLE 3 Unanswered questions surrounding 5-ASA withdrawal

Ulcerative colitis
Safety of 5-ASA monotherapy withdrawal following longer-term remission in higher-risk groups
Safety of 5-ASA withdrawal when on concomitant immunomodulatory
Safety of 5-ASA withdrawal when escalated to newer advanced therapies
Predictive factors and biomarkers for relapse on 5-ASA withdrawal
Crohn's disease
Safety of 5-ASA withdrawal in apparent 5-ASA dependency and following surgical resection

The ongoing use of 5-ASA therapy in UC once patients are escalated to the latest advanced therapies including tofacitinib also awaits clarification, although it seems likely that there will be no clear added benefit, as already reported with anti-TNF and vedolizumab.[46,76]

With an ever increasing array of treatment options, personalisation of approach to IBD therapy is essential and remains a critical unmet research need. Indeed, no biomarkers yet exist either to predict response to 5-ASA therapy or reliably identify when it may be safely withdrawn. The potential cost savings of any clinically useful biomarkers to guide use of 5-ASA therapy would be significant and we suggest that further evaluation of the role of FC should be a particular priority. Furthermore, the use of telemedicine systems, which allow closer monitoring of disease activity, might allow earlier detection of relapse following 5-ASA withdrawal, allowing rapid reintroduction and providing reassurance for both patients and their clinicians (Table 3).[77,78]

In conclusion, although the majority of patients with IBD receive 5-ASA during their disease course, a number of unanswered questions still surround how it should be most effectively used and when it should be withdrawn. Despite this, it is increasingly clear that 5-ASA withdrawal may be safe and indeed appropriate in significant

subsets of patients, with important implications for both health economics and patient experience.

ACKNOWLEDGEMENT

Declaration of personal interests: TC and CFG have no conflicts of interest to declare. EL reports grants from European Commission for BIOCYCLE Research Programme; grants and personal fees from Abbvie, Takeda, Pfizer and Janssen and personal fees from MSD, Ferring, Falk and Celgene. J-FC reports grants from Janssen and Takeda; work as a consultant and/or speaker for AbbVie, Amgen, Arena Pharmaceuticals, Boehringer-Ingelheim, Celgene, Celltrion, Eli Lilly, Enterome, Ferring Pharmaceuticals, Genentech, Janssen, Medimmune, Merck & Co., Nextbiotix, Novartis Pharmaceuticals Corporation, Otsuka Pharmaceutical Development and Commercialization, Inc, Pfizer, Protagonist, Second Genome, Gilead, Seres Therapeutics, Shire, Takeda and Theradiag; and holds stock options with Intestinal Biotech Development and Genfit. JS reports grants from European Commission for BIOCYCLE Research Programme; personal fees from Takeda.

AUTHORSHIP

Guarantor of the article: Professor Jack Satsangi.

Authors' contribution: All authors made substantial contributions to the article. JS, J-FC and EL conceived the idea, TC and CFG drafted the article and JS, J-FC and EL made important revisions and intellectual contributions.

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How to cite this article: Chapman TP, Frias Gomes C, Louis E, Colombel J-F, Satsangi J. Review article: withdrawal of 5-aminosalicylates in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2020;52:73–84. https://doi.org/10.1111/apt.15771