

Review article: maintenance therapy in patients with ulcerative colitis

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SUMMARY

British Society of Gastroenterology guidelines recommend that all patients with ulcerative colitis should receive long-term therapy with a 5-aminosalicylic acid compound to maintain remission.

Recent studies have shown that time spent in remission is longer when the maintenance dose is increased from 1.2 to 2.4 g/day, with patients with extensive disease benefiting most from an increase with dosage. A retrospective analysis also found that the frequency of relapse was lower in patients taking more than the median dose of 5-aminosalicylic acid (1.6 g/day) compared with those taking less than the median dose. Similarly, when 5-aminosalicylic acids are used to induce remission, continuing the induction dosage for an extra 4 weeks prolongs remission and reduces the frequency of relapse. However, patients rarely comply fully with the prescribed dose regimen, which can lead to effective under-dosing.

The recent discovery that 5-aminosalicylic acids may act in ulcerative colitis by activating peroxisome proliferator-activated receptor- γ , a nuclear receptor that plays a role in the control of cell proliferation and apoptosis, has given new impetus to the idea that long-term therapy with 5-aminosalicylic acid may reduce the risk of colorectal cancer. Epidemiological studies are beginning to provide evidence to support this view.

Accumulating evidence suggests that the next revision of the clinical guidelines should suggest life-long doses of 5-aminosalicylic acid of ≥ 2 g/day for maintenance of remission in patients with ulcerative colitis.

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INTRODUCTION

The British Society of Gastroenterology (BSG) guidelines recognize that long-term therapy with a 5-aminosalicylic acid (5-ASA) compound is generally recommended for all patients with ulcerative colitis (UC) to maintain remission, especially those with left-sided or extensive disease.¹ The guidelines do, however, suggest that it may be reasonable to discontinue medication for patients with distal disease who have been in remission for at least 2 years, but add that there is some evidence that continued maintenance therapy reduces the risk of colorectal cancer (CRC).¹ The appropriate treatment recommended in the guidelines is oral 5-ASA (mesalazine) 1–2 g/day or balsalazide 2.5 g/day, although for patients with distal disease, topical therapy may be more appropriate.

DOSAGE

A Cochrane meta-analysis found that the Peto odds ratio for the failure of 5-ASA to maintain clinical or endoscopic remission compared with placebo differed little for doses of 5-ASA <1 g/day, 1–1.9 g/day and ≥ 2 g/day: 0.5 (95% CI: 0.24–1.05); 0.47 (95% CI: 0.36–0.62); 0.47 (95% CI: 0.30–0.75), respectively.² However, the ‘high’ doses in the studies used in this analysis would probably not be regarded as particularly high in today’s clinical practice. This may be one reason why this analysis of relatively old studies suggested that there are few if any reasons for using ‘higher’ doses in order to maintain patients in remission. On the other hand, it is intuitive that higher doses might be better at maintaining remission, and this is backed up by anecdotal evidence, together with some evidence from clinical trials. In a study of Pentasa in 169 patients, the 1-year relapse rate was 33% for those taking 3 g/day compared with 46% in those taking 1.5 g/day ($P = 0.057$). This advantage, although statistically not quite significant, was achieved without any increase in the frequency or severity of adverse effects.³

In another double-blind trial comparing a novel experimental pellet formulation of mesalazine with mesalazine tablets in patients with active UC, it was reported that increasing the dosage to 3 g/day improved the remission rate, irrespective of the formulation that was used.⁴

COMBINATION THERAPY

Better clinical outcomes have been shown to be associated with higher mucosal concentrations of 5-ASA,⁵ and one way of influencing this may be the use of concomitant oral and topical preparations. In a small trial involving patients with refractory disease, all of whom had suffered at least four relapses in the preceding 2 years, increasing their daily dose of 5-ASA to 3.2 g/day or 4.8 g/day and adding topical treatment (5-ASA enema 4 g/day) significantly reduced the number of recurrences from 80 to 8 ($P < 0.0001$). Patients also needed fewer steroids (0 vs. 33; $P < 0.0001$), and experienced fewer days in hospital (0 vs. 93; $P = 0.03$) or out-patient visits (116 vs. 249; $P < 0.0001$).⁶ The investigators concluded that the continuous use of topical 5-ASA reduces the relapse rate in high-risk patients.

In a double-blind, placebo-controlled clinical trial in patients who had experienced at least two relapses in the preceding year, adding an enema of 5-ASA (3 g twice a week) to daily oral dosing with 5-ASA at 1.6 g/day reduced the relapse rate compared with patients who received only oral 5-ASA plus placebo enema (13 of 33 vs. 23 of 36; $P = 0.036$).⁷ Other evidence comes from a case-controlled study in 42 patients that compared oral 5-ASA (1.6 g/day) with oral 5-ASA (1.6 g/day) plus twice weekly 5-ASA enemas (2 g/50 mL). Over the median follow-up time of 6 years there were significantly fewer relapses in the combination-treatment group than in the oral plus placebo-treated group.⁸

TIME IN REMISSION

However impressive the data relating to the number of relapses may be, a key consideration for UC patients is the length of time they spend in remission, rather than the number of relapses they will suffer. Paoluzi *et al.* addressed the question of whether remission was better maintained by 2.4 g/day of 5-ASA than by 1.2 g/day.⁹ They studied 156 patients who were in remission at the start of the study. All had suffered at least one relapse in the previous 5 years and none had previously been treated with corticosteroids. The group treated with 2.4 g/day of 5-ASA by chance had more patients with active disease than the 1.2 g/day group. At 12 months, the relapse rates in the two groups were similar – 74% for 1.2 g/day vs. 70% for the higher dose. However, patients taking the higher dose were in

remission longer than those on the lower dose – 175 days vs. 129 days ($P < 0.001$). For those with extensive disease, the benefit of the higher dose was particularly marked – 143 days vs. 47 days ($P < 0.005$) – although those with distal disease also benefited from the higher dose – 191 days vs. 145 days ($P < 0.009$). However, the 2.4 g/day group contained significantly more patients with a more active disease course; 80% of patients in this dosage group had experienced more than three relapses per year compared with 49% in the 1.2 g/day group. When the results for patients in remission at 12 months were analysed after stratifying for active (>3 relapses per year) vs. less active disease (≤ 3 relapses per year), 2.4 g/day was significantly better than 1.2 g/day (75% vs. 33%, respectively). As with other studies of higher doses of 5-ASA, there was no increase in the frequency of adverse events; only one case was reported (skin rash) in the higher dose group.

FREQUENCY OF RELAPSES

The time between relapses also matters to patients. Blumentals *et al.* addressed this by asking whether increasing the maintenance dose of 5-ASA prolongs remission.¹⁰ They conducted a retrospective analysis of the time to flare up in 566 UC patients taking doses of 5-ASA that were either higher ($n = 310$) or lower ($n = 256$) than the median dose (1.6 g/day). They defined flare as a need to increase the dose or to change the treatment to a glucocorticoid or immunomodulator. They found that the median time to flare up was longer in patients taking >1.6 g/day than in patients taking <1.6 g/day (346 days vs. 256 days; $P = 0.01$).

The evidence, taken together, suggests that higher doses of 5-ASA maintain remission better than lower doses. The challenge to clinicians is to determine what the appropriate dose is for any given patient. In a 12-month follow-up study involving 411 patients whose remission had been induced with 5-ASA alone (178 with mild disease and 233 with moderate–severe disease), patients whose maintenance dose was equal to their induction dose were more than twice as likely to have a normal Physician's Global Assessment (PGA) score at 12 months as patients whose maintenance dose was less than their induction dose (odds ratio: 2.2; 95% CI: 1.4–3.6, $P < 0.01$).¹¹ This is consistent with the view that continuing with the dose used to induce remission is beneficial. Whether this applies to patients whose remissions were achieved through combination

therapy with oral plus topical 5-ASA was addressed in a study by Paoluzi *et al.*¹² They found that an additional 4 weeks of topical treatment did not increase the 12-month remission rate in patients with mild–moderate active UC (50% vs. 51%), although it did appear to reduce the probability of relapse in patients with left-sided colitis (remission rate 66% in patients with left-sided colitis vs. 35% in those with diffuse disease).

ADHERENCE

Even if higher doses of 5-ASA maintain remission better than lower doses, this potential benefit will not be experienced by patients if they do not continue with the treatment. Adherence to prescribed medication is generally better in clinical trials than in real-life practice. A small study (22 patients) sought to discover whether patients would continue with once daily dosing in a real-life clinical practice setting.¹³ Patients were prescribed their daily dose in either a single daily dose ($n = 12$) or in the conventional split-dose manner; either three times a day ($n = 3$) or twice a day ($n = 7$). At 6 months there had been one relapse in each group, and adherence was similar in the two groups (75% in the once daily group vs. 70% in the twice daily/thrice daily group). However, there was a difference in the amount of drug taken; 90% in the once daily group vs. 76% in the multiple-dose group ($P = 0.07$).

Although accumulating evidence suggests that higher doses of 5-ASA achieve better maintenance of remission, there are still some questions that need to be answered by clinical trials. It is not yet clearly established whether maintenance of remission is truly dose-related, and there is no agreed way for the clinician to determine the appropriate dose of 5-ASA for the maintenance of remission. Furthermore, although current evidence shows that increasing the dose does not increase the frequency of adverse effects in the short term, there is no information about the long-term risk of adverse effects associated with higher doses of 5-ASA. Another question that needs to be answered by prospective clinical trials is whether maintenance therapy should routinely combine oral and topical 5-ASA. Finally, we need more information on the acceptability and effectiveness of once daily dosing with 5-ASA. The BSG guidelines state that the recommendations should be reviewed and revised as necessary by late 2007. New evidence is accumulating, and it may already be time to modify the BSG guidelines towards higher doses for maintaining remission

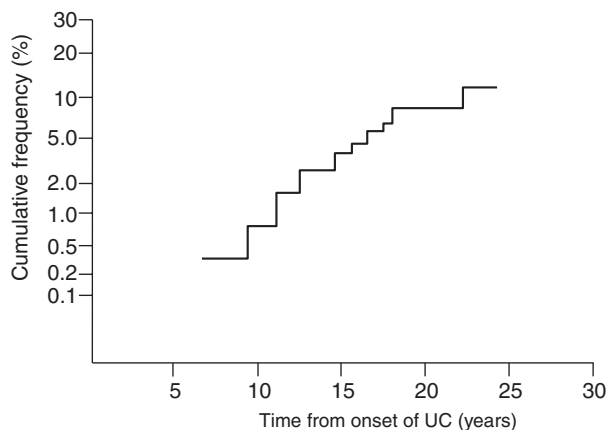


Figure 1. Cumulative frequency of colorectal cancer in patients with ulcerative colitis (UC) as a function of duration of disease [data from Gillen *et al.* (1994)¹⁷].

than are currently advised. What is clearly needed is a prospective, randomized, controlled clinical trial of 5-ASA in patients with UC assessing the long-term effectiveness of higher maintenance-dose strategies vs. current practice (i.e. BSG guidelines).

DOES 5-ASA PROTECT AGAINST COLORECTAL CANCER?

Patients with UC are at increased risk of developing CRC.^{14, 15} Prevention strategies usually rely upon surveillance by regular colonoscopy and when early signs of the development of cancer appear, surgery. One of the risk factors for the development of CRC in patients with UC is the duration of the condition (Figure 1).^{16, 17} It is therefore possible that successful treatment of UC could reduce the risk of CRC.^{1, 18}

However, this possibility has never been definitively demonstrated and 5-ASA has never been licensed as a

chemoprotective agent against CRC in patients with UC. Recent advances in our understanding of the mechanism of action of 5-ASA, which may include activation of the peroxisome proliferator-activated receptor (PPAR)- γ pathway (see P. Desreumaux & S. Ghosh, this supplement), are beginning to suggest a possible rationale for using 5-ASA to prevent the development of CRC in patients with UC.¹⁹ Complex interactions between the Wnt/ β -catenin pathway and PPAR- γ signalling²⁰ and recent data in a mouse model with engrafted human tumour cells (HT29 cells), where 5-ASA reduces the size of tumours by about 80% (an effect that is blocked by GW9662, a competitive antagonist at PPAR- γ), are pertinent in this regard (P. Desreumaux, personal communication).

Evidence-based medicine relies upon evidence of different strengths (Table 1).^{21, 22} When applied to the facts supporting a potential use for 5-ASA in the prevention of CRC in patients with UC, there is a lack of convincing formal evidence (Table 2).^{21, 23–30}

However, ethical considerations mean that it will never be possible to carry out a randomized, placebo-controlled clinical trial to assess the efficacy of 5-ASA in reducing the risk of CRC in patients with UC. Consequently, the only way forward is to assess the evidence already available, much of which is circumstantial. Surveillance strategies and surgery when appropriate are standard practice in most places where access to a high standard of medical care is widely available, and although surveillance is imperfect, it is effective in preventing a large number of CRC cases.¹⁷

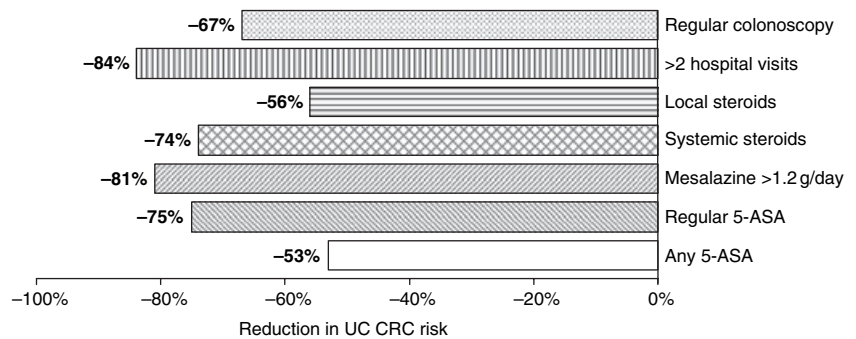
There is also an accumulation of evidence that 5-ASA can reduce the risk of CRC by about 74%, although no single piece of evidence is sufficiently strong to support the conjecture on its own. A recent meta-analysis of nine studies estimated that 5-ASA approximately halved the risk of a patient with UC

Table 1. Evidence-based medicine – the strength of different types of evidence^{21, 22}

Publication type	Evidence	Strength
Meta-analysis or systematic overview of randomized clinical trials	Ia	A
Randomized clinical trials	Ib	
Case-control trials	Ic	B
Controlled, non-randomized trials	IIa	
Cohort studies; diagnostic test (direct diagnostic method)	IIb	C
Case-control trials; diagnostic test (indirect nosographic method); decision analysis; descriptive analysis	III	
Smaller series; case studies; traditional teaching books; traditional overview; expert opinion; editorials	IV	D

Table 2. Evidence that supports a potential role for 5-aminosalicylic acid (5-ASA) in the prevention of cancer in ulcerative colitis (UC) patients

Publication type	Evidence	Strength	Reference
Meta-analysis or systematic overview of randomized clinical trials	Ia	A ✓	21, 30
Randomized clinical trials	Ib		
Case-control trials	Ic ✓		
Controlled, non-randomized trials	IIa	B	
Cohort studies; diagnostic test (direct diagnostic method)	IIb		
Case-control trials; diagnostic test (indirect nosographic method); decision analysis; descriptive analysis	III ✓	C ✓	23-29
Smaller series; case studies; traditional teaching books; traditional overview; expert opinion; editorials	IV	D	

Figure 2. Factors reducing the risk of developing colorectal cancer in patients with ulcerative colitis UC; data from Eaden *et al.* (2000)²⁴.

developing CRC or dysplasia and that the protection increased with the time for which 5-ASA was taken.³⁰ This meta-analysis found only three studies that could be used to assess the effect of dose on protection, one with sulfasalazine and two with 5-ASA itself. The level of protection offered by a daily dose of 0.8 g was less than that offered by 1.2 g/day, although the 95% confidence intervals had a considerable overlap.

Differing results were found, one study found no protection,²³ but a larger study found a significant protective effect, although the investigator identified many potential confounding factors (Figure 2).²⁴ In a cohort study of patients with UC from Copenhagen,³¹⁻³³ the probabilities of developing CRC were lower than those indicated by Eaden *et al.*'s meta-analysis of data from 116 different centres using various treatment strategies³⁴ - 0.2% and 2% after 10 years; 1% and 8% after

20 years; and 3% and 18% after 30 years, respectively. This could in part be explained by the well-established, widespread and routine use of 5-ASA in the Copenhagen region together with a policy of early colectomy for patients with refractory UC.

CONCLUSIONS

The role of 5-ASA in protecting UC patients against CRC is an area of active interest that should be addressed in the next review of the BSG guidelines for the management of UC. Irrespective of whether 5-ASA protects against CRC, the evidence indicates that 5-ASA maintenance therapy should be continued indefinitely. Evolving evidence also indicates that patients on higher dose 5-ASA (>2 g/day) stay in remission for longer than those on conventional doses of 5-ASA.

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