

Systematic review: does concurrent therapy with 5-ASA and immunomodulators in inflammatory bowel disease improve outcomes?

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SUMMARY

Background

With greater use of immunomodulators in inflammatory bowel disease (IBD), it is uncertain whether concurrent therapy with both 5-aminosalicylic acid [5-ASA, mesalazine (mesalamine)] and an immunomodulator is necessary.

Aim

To determine whether concurrent therapy with both 5-ASA and immunomodulator(s) improves outcomes in IBD.

Methods

Systematic review with search terms 'azathioprine, 6-mercaptopurine, thiopurine(s), 5 aminosalicylic acid, mesalazine, inflammatory bowel disease, ulcerative colitis, Crohn's disease, immunosuppressant(s), immunomodulator and methotrexate' in November 2007 to identify clinical trials on concurrent 5-ASA and immunomodulator therapy.

Results

Two small controlled studies were found. Neither showed a benefit on disease control beyond immunomodulator monotherapy. Potential pharmacological interactions exist between 5-ASA and thiopurines. Whilst circumstantial, epidemiological and laboratory evidence suggests that 5-ASA may assist colorectal cancer (CRC) chemoprevention, it may simply be via anti-inflammatory effects. With changes in practice, ethical issues and the long lead-time needed to demonstrate or disprove an effect, no clinical studies can/will directly answer this. The costs of avoiding one CRC in IBD may be as low as 153 times the annual cost of 5-ASA therapy.

Conclusions

It is unclear whether concurrent 5-ASA and immunomodulator therapy improves outcomes of disease control, drug toxicity or compliance. Concurrent therapy of 5-ASA and immunomodulators may decrease CRC risk at 'acceptable' cost.

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INTRODUCTION

Over the last two decades, the trend in inflammatory bowel diseases (IBD) has been to use immunomodulators earlier in the disease course and more frequently.¹ Early use of immunomodulators is, in fact, now recommended in both ulcerative colitis (UC)² and Crohn's disease (CD)³ on the basis that azathioprine (AZA) or mercaptopurine (MP) halves the risk of relapse in both UC and CD.^{4, 5} In particular, a recent Cochrane review calculated an odds ratio for AZA/MP failing to maintain remission in UC of 0.41, with 95% confidence intervals (CIs) from 0.24 to 0.70,⁴ whereas an earlier Cochrane review had already documented an OR for maintenance of remission in CD of 2.16 (95% CI: 1.35–3.47), with a number-needed-to-treat (NNT) of 7.⁵ These data have further provoked a change in practice towards a more widespread use of immunomodulators in IBD. As most patients take mesalazine (mesalamine) preparations [5-aminosalicylic acid (5-ASA)], the question arises whether to combine 5-ASA with thiopurine therapy or to cease 5-ASA as soon as immunomodulation becomes effective.

5-Aminosalicylic acid has been derived from sulphasalazine, which was synthesized more than 50 years ago specifically to treat UC and rheumatoid arthritis.⁶ The linkage of sulphapyridine and salicylate through an azo-bond was viewed as a method of combining antibacterial and anti-inflammatory actions while minimizing gastric irritation. Early therapeutic results from Scandinavia were encouraging. Subsequent controlled trials have confirmed its efficacy in active disease and maintenance of remission.^{7–10} A daily dose of 2 g was considered optimal for maintenance of remission;¹¹ 4 g was recommended during disease flares with the maximum dose being limited by the frequency of adverse drug reactions. Approximately 30% of patients taking sulphasalazine report adverse reactions; many are idiosyncratic, but others are dose-related. Thirty-five years after sulphasalazine discovery, 5-ASA was determined to be the therapeutically active moiety of this drug with proven anti-inflammatory effects in UC with less toxicity.^{12, 13} Recently, once daily 5-ASA dosing demonstrated equivalence to multiple doses^{14–16} not only for the novel multi-matrix (MMX) mesalazine but also for continuous- and pH-dependent release preparations.^{17, 18} This paradigm shift in 5-ASA dosing is expected to increase drug adherence for lifelong therapy.¹⁹ As 5-ASA is the drug of first choice for induction and

maintenance of remission in UC, the question then arises as to whether it should be continued once immunomodulator therapy is established. Doctors tend not to cease any therapy once established and polypharmacy is both common and associated with poorer clinical outcomes in CD, although this may be either cause or effect.^{3, 20} Multiple therapies certainly decrease compliance and <80% adherence to 5-ASA increases the risk of relapse more than five fold (OR: 5.5; 95% CI: 2.3–13.0).^{19, 21, 22} Factors associated with poor compliance include multiple therapies, frequent dosing, young age, being male and single.^{19, 22} Moreover, the fact that insufficient control of inflammation is associated with poor outcome (including colorectal cancer),^{23–25} makes a cogent case for the simplest possible but most effective drug regimen in these patients, especially given the need for long-term or indeed lifelong therapy.

For the purposes of this discussion, concurrent therapy means any standard immunomodulator used for disease control in IBD plus any oral 5-ASA therapy. Due to available data, the immunomodulators referred to are the thiopurines; AZA and MP, although, in theory, this discussion is relevant to any immunomodulator including methotrexate and even to the newer biological therapies, although the data here are currently even sparser.

The role of 5-ASA in newer IBD treatment paradigms

In IBD, treatment has generally been a sequential 'step up' approach where the least toxic and possibly the least potent drugs have been initially used (Figure 1). Despite recent re-evaluation of this paradigm, with a role for a 'top-down' or more intensified approach being promulgated by some,²⁶ 'step up' therapy is still the basic model endorsed in the treatment guidelines promulgated by most major societies including the BSG,²⁷ ECCO^{2, 3} and the ACG.^{28, 29} The results of a recent study in CD,³⁰ however, appear likely to encourage further the paradigm shift towards earlier and more frequent use of immunomodulators and anti-TNF therapy.¹ Combined with the powerful anti-TNF marketing forces, these data may lead to clinician uncertainty as to the ongoing role of 5-ASA once a patient is successfully established on an immunomodulator with good control of disease activity.

In UC, the role of 5-ASA monotherapy is clinically well accepted and proven, with documented efficacy

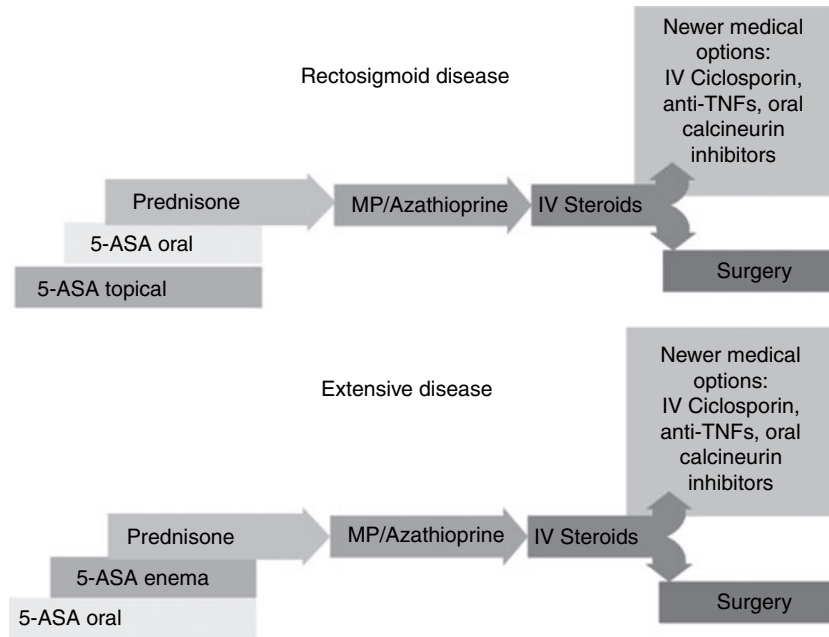


Figure 1. Modified 'Traditional' sequential therapy for ulcerative colitis (adapted from Ref. 29). Rectosigmoid or descending colonic disease: topical 5-aminosalicylic acid (5-ASA) is used in suppository, foam or enema form. Of the oral 5-ASAs, sulphasalazine is the most cost effective, but its use is limited by sulpha-related toxicity. Efficacy of oral 5-ASA is primarily related to the dose delivered to the colonic mucosa. Steroids are often added for those who have failed topical and oral 5-ASA therapy. Mercaptopurine (MP) or azathioprine may be necessary for steroid-dependent or -refractory disease. Finally, surgery, or more aggressive, newer medical therapies may be necessary for refractory disease. Extensive disease: oral 5-ASAs are the first line of therapy. This may be supplemented with topical 5-ASA and steroids. Oral steroids are added for patients who fail 5-ASA therapy (prednisone 40 mg to 60 mg/day). Azathioprine or MP is used for those in whom a steroid taper cannot be achieved. Patients who fail these therapies and who have more severe symptoms, such as fever, abdominal distension, orthostasis and significant anaemia, may require hospitalization and intravenous steroids. If no improvement occurs within 7–10 days of intravenous steroids, consider intravenous ciclosporin or colectomy.²⁹ It should be noted that other medical options including anti-TNF therapy and oral calcineurin inhibitors now also have a role in management.²

in treating mild to moderately active disease, with an odds ratio for failure to achieve clinical improvement of 0.40 (95% CI: 0.30–0.53),³¹ the NNT is 6 for maintenance of remission.³² In clinical practice, 5-ASA is considered the basis of UC therapy as it is also more potent than steroids, has least long-term toxicity and enhances mucosal healing.³³ In CD, the role of 5-ASA therapy is less clear.³⁴ A recent Cochrane systematic review on mesalazine for maintenance of remission in CD has shown no beneficial effect (OR: 1.0; 95% CI: 0.80–1.24).³⁵ However, a more recent meta-analysis on 5-ASA subgroups shows a possible benefit for 5-ASA with pH 7 delivery.³⁶ In the face of this therapeutic uncertainty, many clinicians continue to use 5-ASA in CD,^{37, 38} especially where there is substantial colonic involvement. There is good evidence for 5-ASA in preventing post-operative recurrence, with an NNT from 4–11 depending on the preparation used,³⁶ although

AZA/MP may be more efficacious and the benefit appears to be greater after a second resection. A prospective study randomized 142 patients after ileocolic resection to receive either AZA 2 mg/kg/day or mesalazine 3 g daily for 24 months.³⁹ Clinical (OR: 2.04; 95% CI: 0.89–4.67) and surgical recurrence rates were comparable between groups. However, there was a favourable effect of AZA over 5-ASA in patients who had had a previous resection (OR: 4.83; 95% CI: 1.47–15.8), perhaps marking them as the patients most in need of therapy and most likely to benefit. A further comparison of AZA/MP to 5-ASA therapy for the prevention of post-operative recurrence concurred with these findings⁴⁰ and has led to an established role for AZA/MP in this setting.⁴¹

As addressed earlier, immunomodulators now have an established role in the treatment of both UC and CD.^{2, 3, 27} In particular, they are documented to be

efficacious in the prevention of relapse^{27, 42, 43} and of post-operative recurrence in CD.^{39–41} AZA/MP is primarily indicated for insufficiently controlled inflammation such as steroid-dependent disease.⁴⁴ This is evidenced by its role in allowing withdrawal of steroid therapy.⁴⁵ In such a disease subgroup,⁴⁵ AZA was, in fact, superior to 3.2 g/day of 5-ASA for achieving remission (OR: 4.78; 95% CI: 1.57–14.5 favouring AZA). However, the long lag time from initiating therapy to clinical benefit⁴⁴ makes many immunomodulators (especially thiopurines) unsuitable for the rapid treatment of acute disease flares, as their maximal clinical benefit may take 3–6 months to be achieved and does not appear to be accelerated by front-loading strategies.⁴⁶

It is difficult to be certain of the prevalence of concurrent prescribing of 5-ASA and thiopurines in practice. The Danish Crohn's and Colitis Database⁴⁷ offers perhaps the best snapshot of prescription behaviour in a community-based cohort. At present, they report that 40% of patients with CD and 30% of those with UC are receiving AZA. 60% of these CD patients on AZA receive concurrent 5-ASA, as do 80% of these UC patients (P. Munkholm, pers. comm.). In other major hospital series, approximately 50% of IBD patients are estimated to be on immunomodulators in recent years¹ and it appears likely that a substantial proportion of these are also receiving 5-ASA. These data taken together suggest that up to approximately 25% of all patients receiving specialist care for IBD may be receiving therapy with both an immunomodulator and 5-ASA, making the issue of concurrent therapy an important question worldwide.

METHODS

To address this issue, we conducted a systematic review of the literature for studies which specifically addressed the topic of combined immunomodulator and 5-ASA therapy in IBD. A search of English language articles in PubMed was performed between May and July 2007 and again in November 2007, using the search terms 'azathioprine', '6-mercaptopurine', 'thiopurine(s)', '5-ASA(s)', '5 aminosalicylic acid', 'mesalazine', 'inflammatory bowel disease', 'ulcerative colitis', 'Crohn's disease', 'immunosuppressant(s)', 'immunomodulator(s)' and 'methotrexate', to identify any controlled trials on concurrent therapy. All relevant abstracts were read by one of the authors (JMA). Two papers directly addressing the topic of concurrent

therapy were identified.^{48, 49} Ten studies on the safety of concurrent therapy were also identified.^{49–59} Additional papers were sought by searching the reference lists of these two papers, and from personal knowledge of research in the field by the authors.

The available literature was analysed with respect to five issues:

- Does concurrent therapy with 5-ASA and immunomodulators improve disease control?
- Does concurrent therapy increase drug toxicity?
- Does concurrent therapy change drug adherence?
- Does concurrent therapy improve prevention of colorectal cancer?
- What is the cost-benefit ratio for concurrent therapy?

RESULTS

Using the available studies and referring to other literature where relevant, we examined each of these five issues in turn.

Does concurrent therapy with 5-ASA and immunomodulators improve disease control?

Two studies have directly addressed this issue.^{48, 49} Unfortunately, both are troubled with methodological problems, making a definite answer to this question uncertain.

Mantzaris *et al.* examined steroid-dependent patients with UC who were randomized after induction of remission to either AZA (2.2 mg/kg) alone or AZA with olsalazine (1.5 g/day) for 2 years. To induce remission, 110 patients were treated with a combination of AZA (2.2 mg/kg), oral prednisolone (1 mg/kg), olsalazine (0.5 g/day) and steroid or 5-ASA enemas. Steroids were tapered by 5 mg/week, olsalazine was increased gradually to finally reach 1.5 g/day. Seventy patients could be randomized after remission was achieved and maintained for one additional month without steroids. After 2 years, there was no difference in relapse rates between the two groups [nine of 36 patients (25%) in the combination arm and nine of 34 patients (26.5%) in the monotherapy arm]; however, adverse events (transient leucopenia, diarrhoea or abdominal pain) were more frequent and compliance lower with combination therapy (97% vs. 87%, $P < 0.001$). The authors concluded that patients with steroid-dependent UC are not in need of concurrent 5-ASA therapy.

This is the only prospective study identified on this topic. The main conclusions are somewhat limited for a number of reasons: (i) The study was underpowered as only 70 out of the 100 intended patients were randomized. (ii) Recruitment of patients took almost 10 years indicating that this was a highly selective population of UC patients that may not represent daily practice. (iii) The study design was unusual in the sense that 'steroid-dependent' patients were brought into remission with a maximized combination regimen of high-dose (1 mg/kg), long-term (on average 15–16 weeks) steroids plus AZA plus 5-ASA plus enemas prior to randomization. (iv) The 2-year remission rate in the AZA-only group was unexpectedly high (73.5%). (v) Out of all 5-ASA preparations, olsalazine is known to have the highest rate in adverse events, which can be dose-related. The average olsalazine dosage was as low as 1.25 g/day. Twelve patients (33%) reported an increase in diarrhoea and 15 patients (42%) had abdominal pain; these rates are well beyond what is generally expected for 5-ASA toxicity.

An earlier, retrospective UK study examined 186 AZA-tolerant patients with either UC ($n = 82$) or CD ($n = 104$) in remission. Data on clinical relapse (defined as requirement for surgery or documented symptoms consistent with a relapse necessitating rescue therapy) were gathered via case notes review.⁴⁸ The median follow-up was 4.3 years. Outcomes were compared for CD and UC separately between the AZA plus any 5-ASA ($n = 103$) vs. AZA alone ($n = 83$) group. The mean relapse rate per year was 21% and 19% in those with and without concurrent 5-ASA for UC ($P = 0.69$) and 27% and 30% respectively for CD ($P = 0.97$). Drug toxicity was also comparable between groups. The authors concluded that concurrent 5-ASA therapy did not reduce the relapse rates in IBD patients who were established on AZA and that it did not add toxicity to AZA therapy.

Again, the results need to be interpreted with caution as this was a retrospective chart review and as such included several potential biases: (i) Most importantly, only AZA-tolerant patients who achieved remission were included in the analysis. These patients had been brought into remission either on the combination therapy or on AZA alone. Thereby, the study selects for patients who have already responded well to either of the treatment regimens with little additive toxicity. (ii) The possibility of biologically non-equivalent groups especially as the decision regarding the therapy regimen was made upon clinical judgement.

Those receiving the concurrent 5-ASA may have been incomplete responders to AZA before. (iii) The study was underpowered (the actual group sizes were between 27 and 55 patients) to detect small effects. (iv) Retrospective reviews are known to lack sensitivity to detect subtle differences between groups due to unavailable or incomplete data (such as the stringent definition of relapse).

On the basis of these two studies, one may draw the conclusion that concurrent therapy with a 5-ASA and an immunomodulator is ineffective. The level of evidence, however, is low and the critique to each study considerable. Both studies only looked into maintenance of remission and not control of active disease or endoscopic healing. A conclusive answer falls short due to design quality and patient quantity. A beneficial effect would have to be quite substantial to be detected by the endpoints that were used. Thus, it remains possible that the studies were inadequately powered to reveal clinically relevant differences in outcomes. At this point, we cannot answer whether concurrent therapy with 5-ASA and immunomodulators improves disease control.

Does concurrent therapy increase drug toxicity?

Adverse events associated with 5-ASA therapy are almost always mild and uncommon. Except for olsalazine (as used by Mantzaris *et al.*), 5-ASA compounds rarely lead to the need to withdraw therapy and in general, they do not overlap with the more concerning side effects of thiopurines or methotrexate. One study, cited above, suggested that more adverse events are associated with dual therapy, but these were still within acceptable limits.⁴⁹ However, from a pharmacokinetic point of view, the metabolism of thiopurines is clearly affected by concurrent 5-ASA therapy.^{50, 51} Concurrent therapy leads to increased levels of metabolites of thiopurines^{52, 55} and this has been implicated in thiopurine toxicity in some instances.^{53, 54, 59} Conversely, the withdrawal of 5-ASA from patients on stable and apparently efficacious doses of thiopurines leads to reduction in 6TGN metabolite levels,^{50, 55} but whether this leads to reduced efficacy and is thus clinically significant remains unknown. In practice, these issues and documented changes in metabolite levels have not translated into a large clinical concern. Moreover, from a pragmatic point of view, they do not appear to play a significant role in selecting either drug dose, or monitoring intervals. Likewise, there is

no direct evidence of synergy between these agents in terms of a lower dose of either 5-ASA or immunomodulator being sufficient when co-administered. This may be due to the wide therapeutic range of both 5-ASA and thiopurines or the large variability in thiopurine metabolite levels, which are highly unpredictable after oral dosage. Nevertheless, this confidence may be misplaced. The pharmacokinetic evidence that this interaction matters is strong, but the clinical relevance is not proven, possibly only because it has not been specifically sought. It is difficult to attribute individual relapse episodes to particular changes or gaps in compliance of specific therapy. With the more recent trend to intensify or optimize thiopurine therapy via therapeutic monitoring of metabolites,^{56, 57} this issue of their compatibility may become more complex. At present, there is sufficient longstanding clinical experience to reassure us of their safety when used in combination and the lack of need to make specific dose adjustments simply on this basis. However, it would appear to be prudent to watch for myelosuppression when adding or increasing the dose of 5-ASA in patients on stable dose thiopurines and likewise, patients should be cautioned that relapse on thiopurines may be more likely if 5-ASA is discontinued, although this is not yet proven.

Does concurrent therapy change drug adherence?

The complexity in drug regimes has the potential to impair adherence to therapy. Medication non-adherence (compliance <80%) is associated with an increased rate of relapse.²¹ The specific issue of whether concurrent 5-ASA and immunomodulator therapy impairs adherence has not been studied, although some indirect evidence on the topic exists. The study on concurrent therapy from Greece⁴⁹ found combination therapy to lead to decreased compliance. This is probably caused by the type of 5-ASA compound and its adverse event profile. The retrospective design of the UK study⁴⁸ precludes any results on compliance. Interestingly, one study on medication taking behaviour in IBD patients found that oral mesalazine and AZA were the two drugs with the poorest compliance;⁶⁰ whether this is because they were the two most commonly prescribed drugs remains unknown, but it does emphasize the size of the potential problem with compliance. Patients on immunomodulators usually have better compliance than those

not requiring them,²² perhaps as a marker of severe disease or better understanding of consequences of therapeutic failure. Although it is unknown whether the co-prescription of 5-ASA in this group has any additional effect on adherence, it does seem likely as more complex drug prescribing regimens and higher total pill counts are well documented to decrease medication adherence.⁶¹ The compliance issue may become less of an issue with the new once-daily dosing regimen of 5-ASA.^{14–18}

Does concurrent therapy improve prevention of colorectal cancer?

There is a long-standing acceptance that UC is associated with an increased risk of CRC with the first well documented report appearing in 1925.⁶² Importantly, in 1994, some UK data were published showing equivalent high CRC risk with extensive Crohn's colitis.^{63, 64} Many other studies now confirm this risk for extensive longstanding colitis, although the magnitude varies greatly in different cohorts. A meta-analysis revealed a cumulative CRC risk of 18% in UC patients after 30 years of disease.⁶⁵

Such high CRC rates dropped within the next couple of years.^{66–70} This may possibly have been a result of an active approach to both medical and surgical treatment (such as a cumulative colectomy rate of 32%) as well as active surveillance programmes, or of the increasingly widespread use of 5-ASA maintenance therapy in colitis. Within IBD population, however, there are five distinct features, which are associated with an extraordinarily high risk of CRC (Figure 2): (i) extensive colonic disease, (ii) early onset of colitis/long disease duration, (iii) severity of inflammation, (iv) family history of CRC and (v) the presence of primary sclerosing cholangitis (PSC).^{23, 70–74}

The first three of these features are directly related to the burden of inflammation, while family history is probably caused by genetic (inherited) factors. The mechanism of how the coexistence of PSC enhances colon carcinogenesis in IBD is currently obscure. The clinical importance, however, is high as this specific subgroup is at the highest risk of all (every second patient was reported to develop CRC after 25 years of disease) and warrants special consideration.⁷⁴

Certainly, the persistence of clinically active disease or mucosal inflammation appears to be a significant risk factor for development of CRC. The groups from St Mark's and Minnesota have shown that histological

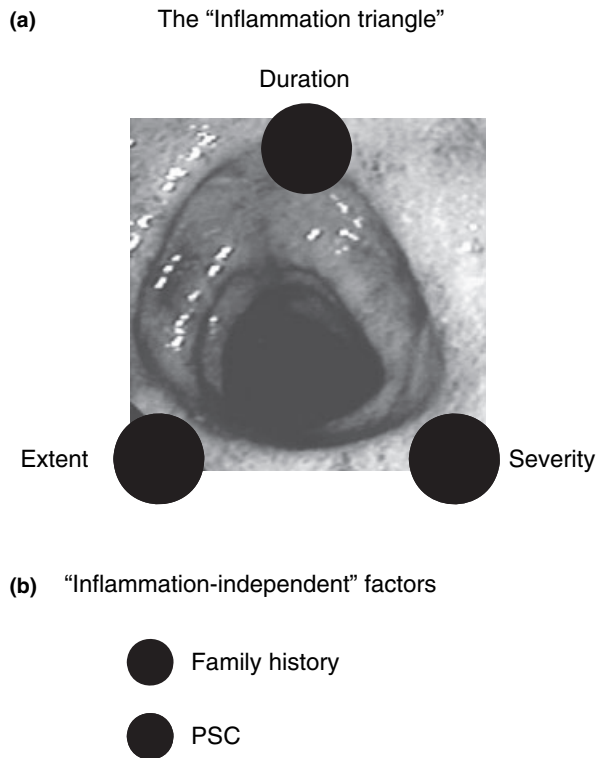


Figure 2. Colorectal cancer high-risk groups within the colitis population. Two types of risk profiles exist: inflammation-related factors (a) and inflammation-unrelated characteristics (b). The most important risk factor is presence of primary sclerosing cholangitis (PSC).

severity of inflammation is associated with a greater risk of neoplasia.^{23, 67} In support of this finding, both percentage of time with clinically active disease and >12 months of continuous symptoms have also been associated with an increased risk of neoplasia (OR per 5% increase in time = 1.2, 95% CI: 1–1.4 and OR: 3.2, 95% CI: 1.2–8.6 respectively).⁷⁵ This latter study was performed as a nested case-control study in two well-defined population-based IBD cohorts (Copenhagen County, Denmark, and Olmsted County, Minnesota) where 43 cases of IBD associated CRC were matched on six criteria to 1–3 controls each ($n = 102$). Thus, the finding is likely to be widely representative of 'real world' patients. Lending further credence to this relationship between disease activity and CRC is the finding that the presence of pseudopolyps (a marker of severity of inflammation) doubles the risk of CRC development (OR: 2.5; 95% CI: 1.4–4.6).⁷⁶ Another dimension of intestinal inflammation is the extent and the duration of disease both of which are also

important risk factors associated with CRC development.

A second possible explanation for the observed decrease in CRC risk in recent decades may be the more widespread use of 5-ASA preparations. Indeed, in the last several years, reports have been emerging which suggest that 5-ASA therapy is associated with a protective effect against the development of CRC in longstanding colitis. Although not all reports agree,⁷⁷ large studies²⁵ and a meta-analysis⁷⁸ are generally regarded as very persuasive in this regard. The putative predominant mechanism responsible for the enhanced risk of CRC in IBD is chronic mucosal inflammation.⁷⁹ Thus, the control of mucosal inflammation itself by 5-ASA seems likely to be important in CRC prevention. It might then be anticipated that any drug which successfully maintains remission in patients with IBD will be associated with reduced risk of CRC. Indeed, a recent study has suggested that thiopurines might also be protective.⁸⁰ In other words, the observation that 5-ASA protects from CRC might reflect purely maintenance of disease remission rather than molecular effects independent of its anti-inflammatory properties.

In the very recent past, inflammation-independent 5-ASA activities have become a focus of research (Table 1). Amongst the variety of 5-ASA's anti-cancer activities, the improvement of replication fidelity^{81, 82} and CpG demethylation⁸³ are considered mechanistically important as these are central in the process of colon carcinogenesis. At present, the underlying molecular effects are the subject of several research programmes aiming for novel anti-cancer drugs. The inflammation-independent chemopreventive activities of 5-ASA further support its role in CRC prevention and strengthen the evidence from epidemiological studies.

With the existing data,²⁵ the long time-lag for a measurable effect and the ethical issues involved, it is not possible to perform a randomized clinical trial to

Table 1. Anti-cancer activities of 5-aminosalicylic acid^{81–90}

Oxygen scavenging
Inhibition of β -catenin
Activation of PPAR-gamma
Inhibition of EGF-R signalling
CpG demethylation
Cell cycle checkpoint activation
Increase in DNA replication fidelity

evaluate stringently the role of 5-ASA in CRC prevention. At this point, 5-ASA-mediated protection from CRC is generally accepted and should be utilized at least in CRC high risk groups. Endoscopic or histological presence of inflammation during surveillance colonoscopy should trigger 5-ASA initiation or a 5-ASA dose increase in patients even if they are in clinical remission.

What is the cost-benefit ratio for concurrent therapy?

The cost side is known, 5-ASA therapy is not inexpensive and long-term treatment is needed. The benefit, therefore, would need to be substantial to justify it purely on chemoprevention grounds, rather than as therapy for disease control and maintenance of remission. Although the data are flawed, some estimates can be made: if the CRC rate is 18% at 20 years⁶⁵ and one gets a reduction to 5.4% (OR: 0.28)⁷⁸ with regular use of a 'good' (2 g/day) dose of 5-ASA, this would mean saving 13/100 people from CRC over 20 years at a cost of 100 pts × 20 years × local annual cost of 5-ASA/13 pts, which comes to 153 × annual cost of therapy per CRC saved. Obviously, the equation is more complicated than this with the necessary inclusion of monitoring, possible adverse reactions and some patients coming to surgery before encountering the risk of CRC at 20 years. Additionally, the benefit may be markedly less and the cost higher, if the apparent reduction in IBD-related CRC is due to factors other than 5-ASA therapy or if the protective effect is due simply to disease control or if the original risk of CRC in colitis was substantially overestimated.

CONCLUSIONS

Current evidence from clinical trials is insufficient to conclude that 5-ASA has no additional benefit over monotherapy with immunosuppressants for control of

intestinal inflammation either in UC or in CD. Apart from some inhibition of thiopurine metabolism by 5-ASA (that is of uncertain but potentially important clinical significance) immunomodulators and 5-ASA are compatible as concurrent therapy. There is general evidence that concurrent therapy is associated with impaired drug adherence, although whether this applies to modern once daily dosage of 5-ASA and immunomodulators is uncertain. At present, the most persuasive reason to use 5-ASA concurrently to immunomodulators is for prevention of CRC in patients with UC or Crohn's colitis. The cost per CRC prevented may be as low as 153 times the annual cost of 5-ASA, but this most likely over-estimates their benefit, if disease is well controlled. The chemopreventive value of 5-ASA is justified in CRC high risk groups and in patients with incomplete mucosal healing on surveillance colonoscopies.

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REFERENCES

- 1 Cosnes J, Nion-Larmurier I, Beaugerie L, Afchain P, Tiret E, Gendre JP. Impact of the increasing use of immunosuppressants in Crohn's disease on the need for intestinal surgery. *Gut* 2005; 54: 237-41.
- 2 Stange EF, Travis SP, Vermeire S, *et al.* European Consensus on the diagnosis and management of ulcerative colitis: definitions and diagnosis. *J Crohn's Colitis* 2008; 2: 1-23.
- 3 Travis SP, Stange EF, Lemann M, *et al.* European evidence based consensus on the diagnosis and management of Crohn's disease: current management. *Gut* 2006; 55(Suppl. 1): 116-35.
- 4 Timmer A, McDonald JW, Macdonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative

- colitis. *Cochrane Database Syst Rev* 2007; 1: CD000478.
- 5 Pearson DC, May GR, Fick G, Sutherland LR. Azathioprine for maintaining remission of Crohn's disease. *Cochrane Database Syst Rev* 2000; 2: CD000067.
 - 6 Svartz N. Salazopyrin, a new sulfanilamide preparation: A. Therapeutic results in rheumatic polyarthritis. B. Therapeutic results in ulcerative colitis. C. Toxic manifestations in treatment with sulfanilamide preparation. *Acta Med Scand* 1942; 110: 557-90.
 - 7 Baron JH, Connell A, Lennard-Jones J, Jones F. Sulphasalazine and salicylazosulphadimidine in ulcerative colitis. *Lancet* 1962; 3: 1094-6.
 - 8 Truelove SC, Watkinson G, Draper G. Comparison of corticosteroid and sulphasalazine therapy in ulcerative colitis. *Br Med J* 1962; 29: 1708-11.
 - 9 Dick AP, Grayson MJ, Carpenter RG, Petrie A. Controlled trial of sulphasalazine in the treatment of ulcerative colitis. *Gut* 1964; 5: 437-42.
 - 10 Dissanayake AS, Truelove SC. A controlled therapeutic trial of long-term maintenance treatment of ulcerative colitis with sulphasalazine (Salazopyrin). *Gut* 1973; 14: 923-6.
 - 11 Azad Khan AK, Howes DT, Piris J, Truelove SC. Optimum dose of sulphasalazine for maintenance treatment in ulcerative colitis. *Gut* 1980; 21: 232-40.
 - 12 Azad Khan AK, Piris J, Truelove SC. An experiment to determine the active therapeutic moiety of sulphasalazine. *Lancet* 1977; 2: 892-5.
 - 13 Sutherland LR, May GR, Shaffer EA. Sulphasalazine revisited: a meta-analysis of 5-aminosalicylic acid in the treatment of ulcerative colitis. *Ann Intern Med* 1993; 118: 540-9.
 - 14 Lichtenstein GR, Kamm MA, Boddu P, et al. Effect of once- or twice-daily MMX mesalamine (SPD476) for the induction of remission of mild to moderately active ulcerative colitis. *Clin Gastroenterol Hepatol* 2007; 5: 95-102.
 - 15 Kamm MA, Sandborn WJ, Gassull M, et al. Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. *Gastroenterology* 2007; 132: 66-75.
 - 16 Kamm MA, Lichtenstein GR, Sandborn WJ, et al. Randomised trial of once- or twice-daily MMX mesalazine for maintenance of remission in ulcerative colitis. *Gut* 2008; 57: 893-902.
 - 17 Kruis W, Gorelov A, Kiudelis G, et al. Once daily dosing of 3 g mesalamine (Salofalk (R) granules) is therapeutic equivalent to a three-times daily dosing of ig mesalamine for the treatment of active ulcerative colitis. *Gastroenterology* 2008; 132: A130-1.
 - 18 Dignass A, Vermeire S, Adamek H, et al. Improved remission rates from once- versus twice-daily mesalazine (Pentasa) granules for the maintenance of remission in ulcerative colitis: results from a multinational randomised controlled trial [abstract]. *Endoscopy* 2007; 37: A46-7.
 - 19 Kane SV. Systematic review: adherence issues in the treatment of ulcerative colitis. *Aliment Pharmacol Ther* 2006; 23: 577-85.
 - 20 Cross RK, Wilson KT, Binion DG. Polypharmacy and Crohn's disease. *Aliment Pharmacol Ther* 2005; 21: 1211-6.
 - 21 Kane S, Huo D, Aikens J, Hanauer S. Medication nonadherence and the outcomes of patients with quiescent ulcerative colitis. *Am J Med* 2003; 114: 39-43.
 - 22 Ediger JP, Walker JR, Graff L, et al. Predictors of medication adherence in inflammatory bowel disease. *Am J Gastroenterol* 2007; 102: 1417-26.
 - 23 Rutter M, Saunders B, Wilkinson K, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology* 2004; 126: 451-9.
 - 24 Velayos FS, Loftus EV Jr, Jess T, et al. Predictive and protective factors associated with colorectal cancer in ulcerative colitis: a case-control study. *Gastroenterology* 2006; 130: 941-9.
 - 25 van Staa TP, Card T, Logan RF, Leufkens HG. 5-Aminosalicylate use and colorectal cancer risk in inflammatory bowel disease: a large epidemiological study. *Gut* 2005; 54: 1573-8.
 - 26 Oldenburg B, Hommes D. Biological therapies in inflammatory bowel disease: top-down or bottom-up? *Curr Opin Gastroenterol* 2007; 23: 395-9.
 - 27 Carter MJ, Lobo AJ, Travis SP. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2004; 53(Suppl. 5): V1-16.
 - 28 Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults. American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 1997; 92: 204-11.
 - 29 Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2004; 99: 1371-85.
 - 30 D'Haens G, Baert F, Van Assche G, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 2008; 371: 660-7.
 - 31 Sutherland L, Macdonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2006; 2: CD000544.
 - 32 Bebb JR, Scott BB. How effective are the usual treatments for ulcerative colitis? *Aliment Pharmacol Ther* 2004; 20: 143-9.
 - 33 Hanauer SB. Review article: evolving concepts in treatment and disease modification in ulcerative colitis. *Aliment Pharmacol Ther* 2008; 27(Suppl. 1): 15-21.
 - 34 Egan LJ, Sandborn WJ. Advances in the treatment of Crohn's disease. *Gastroenterology* 2004; 126: 1574-81.
 - 35 Akobeng AK, Gardener E. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's Disease. *Cochrane Database Syst Rev* 2005; 1: CD003715.
 - 36 Steinhart AH, Forbes A, Mills EC, Rodgers-Gray BS, Travis SP. Systematic review: the potential influence of mesalazine formulation on maintenance of remission in Crohn's disease. *Aliment Pharmacol Ther* 2007; 25: 1389-99.
 - 37 Blomqvist P, Feltelius N, Lofberg R, Ekbohm A. A 10-year survey of inflammatory bowel diseases-drug therapy, costs and adverse reactions. *Aliment Pharmacol Ther* 2001; 15: 475-81.
 - 38 Gearry RB, Ajlouni Y, Nandurkar S, Iser JH, Gibson PR. 5-Aminosalicylic acid (mesalazine) use in Crohn's disease: a survey of the opinions and practice of Australian gastroenterologists. *Inflamm Bowel Dis* 2007; 13: 1009-15.
 - 39 Ardizzone S, Maconi G, Sampietro GM, et al. Azathioprine and mesalamine for prevention of relapse after conservative surgery for Crohn's disease. *Gastroenterology* 2004; 127: 730-40.
 - 40 Hanauer SB, Korelitz BI, Rutgeerts P, et al. Postoperative maintenance of Crohn's disease remission with 6-mercaptopurine, mesalamine, or placebo: a 2-year trial. *Gastroenterology* 2004; 127: 723-9.
 - 41 Lemann M. Review article: can postoperative recurrence in Crohn's disease be prevented? *Aliment Pharmacol Ther* 2006; 24(Suppl. 3): 22-8.
 - 42 Candy S, Wright J, Gerber M, Adams G, Gerig M, Goodman R. A controlled double blind study of azathioprine in the management of Crohn's disease. *Gut* 1995; 37: 674-8.
 - 43 Fernandez-Banares F, Bertran X, Esteve-Comas M, et al. Azathioprine is useful in maintaining long-term remission induced

- by intravenous cyclosporine in steroid-refractory severe ulcerative colitis. *Am J Gastroenterol* 1996; **91**: 2498–9.
- 44 Sandborn W, Sutherland L, Pearson D, May G, Modigliani R, Prantera C. Azathioprine or 6-mercaptopurine for inducing remission of Crohn's disease. *Cochrane Database. Syst Rev* 2000; **2**: CD000545.
- 45 Ardizzone S, Maconi G, Russo A, Imbesi V, Colombo E, Bianchi PG. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. *Gut* 2006; **55**: 47–53.
- 46 Sandborn WJ, Tremaine WJ, Wolf DC, *et al.* Lack of effect of intravenous administration on time to respond to azathioprine for steroid-treated Crohn's disease. North American Azathioprine Study Group. *Gastroenterology* 1999; **117**: 527–35.
- 47 Vind I, Riis L, Jess T, *et al.* Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003–2005: a population-based study from the Danish Crohn colitis database. *Am J Gastroenterol* 2006; **101**: 1274–82.
- 48 Campbell S, Ghosh S. Effective maintenance of inflammatory bowel disease remission by azathioprine does not require concurrent 5-aminosalicylate therapy. *Eur J Gastroenterol Hepatol* 2001; **13**: 1297–301.
- 49 Mantzaris GJ, Sfakianakis M, Archavlis E, *et al.* A prospective randomized observer-blind 2-year trial of azathioprine monotherapy versus azathioprine and olsalazine for the maintenance of remission of steroid-dependent ulcerative colitis. *Am J Gastroenterol* 2004; **99**: 1122–8.
- 50 Dewit O, Vanheuverzwyn R, Desager JP, Horsmans Y. Interaction between azathioprine and aminosalicylates: an in vivo study in patients with Crohn's disease. *Aliment Pharmacol Ther* 2002; **16**: 79–85.
- 51 Szumlanski CL, Weinshilboum RM. Sulphasalazine inhibition of thiopurine methyltransferase: possible mechanism for interaction with 6-mercaptopurine and azathioprine. *Br J Clin Pharmacol* 1995; **39**: 456–9.
- 52 Hande S, Wilson-Rich N, Bousvaros A, *et al.* 5-aminosalicylate therapy is associated with higher 6-thioguanine levels in adults and children with inflammatory bowel disease in remission on 6-mercaptopurine or azathioprine. *Inflamm Bowel Dis* 2006; **12**: 251–7.
- 53 Gilissen LP, Derijks LJ, Verhoeven HM, *et al.* Pancytopenia due to high 6-methylmercaptapurine levels in a 6-mercaptopurine treated patient with Crohn's disease. *Dig Liver Dis* 2007; **39**: 182–6.
- 54 Lewis LD, Benin A, Szumlanski CL, *et al.* Olsalazine and 6-mercaptopurine-related bone marrow suppression: a possible drug-drug interaction. *Clin Pharmacol Ther* 1997; **62**: 464–75.
- 55 Gilissen LP, Bierau J, Derijks LJ, *et al.* The pharmacokinetic effect of discontinuation of mesalazine on mercaptopurine metabolite levels in inflammatory bowel disease patients. *Aliment Pharmacol Ther* 2005; **22**: 605–11.
- 56 Derijks LJ, Gilissen LP, Engels LG, *et al.* Pharmacokinetics of 6-mercaptopurine in patients with inflammatory bowel disease: implications for therapy. *Ther Drug Monit* 2004; **26**: 311–8.
- 57 Derijks LJ, Gilissen LP, Hooymans PM, Hommes DW. Review article: thiopurines in inflammatory bowel disease. *Aliment Pharmacol Ther* 2006; **24**: 715–29.
- 58 Lowry PW, Szumlanski CL, Weinshilboum RM, Sandborn WJ. Balsalazide and azathioprine or 6-mercaptopurine: evidence for a potentially serious drug interaction. *Gastroenterology* 1999; **116**: 1505–6.
- 59 Lowry PW, Franklin CL, Weaver AL, *et al.* Leucopenia resulting from a drug interaction between azathioprine or 6-mercaptopurine and mesalamine, sulphasalazine, or balsalazide. *Gut* 2001; **49**: 656–64.
- 60 Bernal I, Domenech E, Garcia-Planella E, *et al.* Medication-taking behavior in a cohort of patients with inflammatory bowel disease. *Dig Dis Sci* 2006; **51**: 2165–9.
- 61 Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 2001; **23**: 1296–310.
- 62 Crohn B, Rosenberg H. The sigmoidoscopic picture of chronic ulcerative colitis (non-specific). *Am J Med Sci* 1925; **170**: 220–7.
- 63 Gillen CD, Andrews HA, Prior P, Allan RN. Crohn's disease and colorectal cancer. *Gut* 1994; **35**: 651–5.
- 64 Gillen CD, Walmsley RS, Prior P, Andrews HA, Allan RN. Ulcerative colitis and Crohn's disease: a comparison of the colorectal cancer risk in extensive colitis. *Gut* 1994; **35**: 1590–2.
- 65 Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 2001; **48**: 526–35.
- 66 Langholz E, Munkholm P, Davidsen M, Binder V. Colorectal cancer risk and mortality in patients with ulcerative colitis. *Gastroenterology* 1992; **103**: 1444–51.
- 67 Jess T, Loftus EV Jr, Velayos FS, *et al.* Risk of intestinal cancer in inflammatory bowel disease: a population-based study from olmsted county, Minnesota. *Gastroenterology* 2006; **130**: 1039–46.
- 68 Winther KV, Jess T, Langholz E, Munkholm P, Binder V. Long-term risk of cancer in ulcerative colitis: a population-based cohort study from Copenhagen County. *Clin Gastroenterol Hepatol* 2004; **2**: 1088–95.
- 69 Lakatos L, Mester G, Erdelyi Z, *et al.* Risk factors for ulcerative colitis-associated colorectal cancer in a Hungarian cohort of patients with ulcerative colitis: results of a population-based study. *Inflamm Bowel Dis* 2006; **12**: 205–11.
- 70 Rutter MD, Saunders BP, Wilkinson KH, *et al.* Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. *Gastroenterology* 2006; **130**: 1030–8.
- 71 Ekbohm A, Helmick C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer. A population-based study. *N Engl J Med* 1990; **323**: 1228–33.
- 72 Gyde SN, Prior P, Allan RN, *et al.* Colorectal cancer in ulcerative colitis: a cohort study of primary referrals from three centres. *Gut* 1988; **29**: 206–17.
- 73 Canavan C, Abrams KR, Mayberry J. Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn's disease. *Aliment Pharmacol Ther* 2006; **23**: 1097–104.
- 74 Broome U, Lofberg R, Veress B, Eriksson LS. Primary sclerosing cholangitis and ulcerative colitis: evidence for increased neoplastic potential. *Hepatology* 1995; **22**: 1404–8.
- 75 Jess T, Loftus EV Jr, Velayos FS, *et al.* Risk factors for colorectal neoplasia in inflammatory bowel disease: a nested case-control study from Copenhagen county, Denmark and Olmsted county, Minnesota. *Am J Gastroenterol* 2007; **102**: 829–36.
- 76 Velayos FS, Loftus EV Jr, Jess T, *et al.* Predictive and protective factors associated with colorectal cancer in ulcerative colitis: a case-control study. *Gastroenterology* 2006; **130**: 1941–9.
- 77 Bernstein CN, Blanchard JF, Metge C, Yogendran M. Does the use of 5-aminosalicylates in inflammatory bowel disease prevent the development of colorectal

- cancer? *Am J Gastroenterol* 2003; 98: 2784–8.
- 78 Velayos FS, Terdiman JP, Walsh JM. Effect of 5-aminosalicylate use on colorectal cancer and dysplasia risk: a systematic review and metaanalysis of observational studies. *Am J Gastroenterol* 2005; 100: 1345–53.
- 79 Boland CR, Luciani MG, Gasche C, Goel A. Infection, inflammation, and gastrointestinal cancer. *Gut* 2005; 54: 1321–31.
- 80 Strelvel EL, Irvine EJSF, Steinhart AH. Immunosuppressives and surgery reduce risk of GI cancers in patients with Crohn's disease: a case control study. *Can J Gastroenterol* 2005; 19(Suppl. B): 5B.
- 81 Gasche C, Goel A, Natarajan L, Boland CR. Mesalazine improves replication fidelity in cultured colorectal cells. *Cancer Res* 2005; 65: 3993–7.
- 82 Luciani MG, Campregher C, Fortune JM, Kunkel TA, Gasche C. 5-ASA affects cell cycle progression in colorectal cells by reversibly activating a replication checkpoint. *Gastroenterology* 2007; 132: 221–35.
- 83 Goel A, Nagasaka T, Gasche C, Boland CR. Chemopreventive effects of mesalazine through inhibition of DNA methyltransferases and reactivation of methylation-silenced genes in human colon cancer cells. *Gastroenterology* 2007; 1: A39.
- 84 Joshi R, Kumar S, Unnikrishnan M, Mukherjee T. Free radical scavenging reactions of sulfasalazine, 5-aminosalicylic acid and sulfapyridine: mechanistic aspects and antioxidant activity. *Free Radic Res* 2005; 39: 1163–72.
- 85 Bos CL, Diks SH, Hardwick JC, Walburg KV, Peppelenbosch MP, Richel DJ. Protein phosphatase 2A is required for mesalazine-dependent inhibition of Wnt/beta-catenin pathway activity. *Carcinogenesis* 2006; 27: 2371–82.
- 86 Rousseaux C, Lefebvre B, Dubuquoy L, *et al.* Intestinal antiinflammatory effect of 5-aminosalicylic acid is dependent on peroxisome proliferator-activated receptor-gamma. *J Exp Med* 2005; 201: 1205–15.
- 87 Schwab M, Reynders V, Loitsch S, *et al.* PPAR{gamma} is involved in mesalazine-mediated induction of apoptosis and inhibition of cell growth in colon cancer cells. *Carcinogenesis* 2008; 29: 1407–14.
- 88 Monteleone G, Franchi L, Fina D, *et al.* Silencing of SH-PTP2 defines a crucial role in the inactivation of epidermal growth factor receptor by 5-aminosalicylic acid in colon cancer cells. *Cell Death Differ* 2006; 13: 202–11.
- 89 Reinacher-Schick A, Schoeneck A, Graeven U, Schwarte-Waldhoff I, Schmiegel W. Mesalazine causes a mitotic arrest and induces caspase-dependent apoptosis in colon carcinoma cells. *Carcinogenesis* 2003; 24: 443–51.
- 90 Stolfi C, Fina D, Caruso R, *et al.* Mesalazine negatively regulates CDC25A protein expression and promotes accumulation of colon cancer cells in S phase. *Carcinogenesis* 2008; 29: 1258–66.