Update on the role of modified release mesalamine in the management of ulcerative colitis and Crohn’s disease

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Abstract: 5-aminosalicylates (5-ASA) remain a key first-line therapy for patients with ulcerative colitis (UC). A range of 5-ASA preparations is available and Eudragit-S® coated modified release formulations of mesalamine, such as Asacol®, remain among the most popular choices. We here review the current understanding of the mechanism of action of 5-ASA in inflammatory bowel disease. We evaluate evidence supporting the efficacy and safety of modified release mesalamine for both induction and remission maintenance in UC, including a review of the data from the recent ASCEND studies. We also examine the controversial issue of the role of mesalamine in treatment of Crohn’s disease (CD) and highlight data supporting its use following surgically induced remission of CD. Evidence supporting the use of mesalamine as prophylaxis for colorectal cancer and dysplasia will be considered. Finally, recent developments in our understanding of how to use modified release mesalamine in a safe and cost-effective manner are evaluated, including discussion of the importance of studying patient non-adherence as a key component of future studies in this area.

Keywords: mesalamine (mesalazine), 5-aminosalicylate, ulcerative colitis, Crohn’s disease, modified release

Introduction
The therapeutic activity of 5-aminosalicylates (5-ASA) in inflammatory bowel disease (IBD) was first demonstrated by the use of orally administered sulfasalazine (which is cleaved to its constituent 5-ASA and sulfapyridine moieties by the action of colonic microflora). While sulfasalazine is effective for induction and remission of maintenance in ulcerative colitis (UC), it is poorly tolerated (particularly at higher doses). Most toxicity results from the sulfa component, which is largely systemically absorbed, while 5-ASA remains predominantly in the colon. Indeed it was this observation that led to the hypothesis that 5-ASA was the active therapeutic component and this was confirmed in studies using enemas of the individual constituents. Several alternative strategies have been employed to direct delivery of 5-ASA to the distal intestine including the use of carrier molecules (as employed in the formulation of balsalazide) or the use of dimeric 5-ASA such as olsalazine; however arguably the more popular strategy has been the use of altered release formulations of mesalamine (or mesalazine), the name used for 5-ASA when it is employed alone as a drug. Two broad formulation strategies have been employed; the use of ethyl cellulose coated microgranules employed in the prototype prolonged release formulation Pentasa® and the use of acrylic enteric coating in formulations such as Asacol®, Claversal® and Salofalk®. We will here focus attention more specifically on Eudragit-S® coated modified release mesalamine
marketed as Asacol® or Asacolon®. We will review briefly
data relating to the pharmacology of this preparation before
focusing attention on the pharmacology of its use for both induction
and remission maintenance in UC and Crohn’s disease (CD).
We will also look at data on safety and tolerability and the
evidence to support 5-ASA use for chemoprophylaxis of
colorectal neoplasia. We will concentrate particular attention
on recent studies and conclude with a summary of our
views on the place of modified release mesalamine in current
IBD therapy.

Pharmacology of modified release mesalamine
Modified release mesalamine (Asacol®) ensures active drug
reaches its principal site of action in the colon by use of a
delivery system that involves coating of the active drug in a
synthetic polymer. The coating consists of an 80 to 130 µm
layer of Eudragit-S®, a resin containing methacrylic acid
and methyl methacrylic acid in a 1:2 ratio. This acrylic resin
layer is soluble at a pH of 7 or greater, with the result that
drug release therefore occurs in the terminal ileum, the initial
site during transit through the gastro-intestinal tract where
luminal pH exceed neutral. While significant variations in
colonic 5-ASA delivery between agents have been observed,
modified release mesalamine appears to achieve satisfactory
concentrations of mesalamine in colonic tissue. Significant
systemic 5-ASA absorption occurs with all oral prepara-
tions and absorbed mesalamine is principally inactivated by
acetylation in the liver with subsequent urinary excretion of
metabolites. Most orally administered modified release
mesalamine is, however, excreted by the fecal route. The
pharmacokinetics of delayed release mesalaminex do not
appear altered by the use of acid suppressants and are not
altered significantly in patients with diarrhea.

Mechanism of action of 5-ASA
The mechanism of action of mesalamine is far from entirely
understood, although a growing understanding of the molecu-
lar action of 5-ASA agents has been emerging. It is now well
established that 5-ASA drugs have effects on the production
and action of a number of key pro-inflammatory cytokines.
5-ASA drugs appear to impair binding of interferon-gamma
(IFN-γ) to its receptor and disrupt the action of this key
pro-inflammatory chemokine, including blocking of its
detrimental effects on gut barrier function. 5-ASA agents
reduce ex vivo production of interleukin-1 beta (IL-1β) in
IBD mucosal biopsies and also appear to impair the production of
interleukin 2 (IL-2) with consequent effects on proliferation of
t-lymphocytes. In addition to their effects on key cytokines,
alterations in other key mediators of inflammation have also
been described. 5-ASA agents have been noted to have a
significant impact on production and activity of eicosanoids
– arachidonic acid-derived signaling molecules with important
vascular and immunoregulatory effects. 5-aminosalicylic acid
reduced ex vivo generation of PGE₂ and LTB₄ by colonic
mucosa from UC patients in one study and was noted to
reduce LTB₄ in another study (where no change in PGE₂ was
detected) with an associated reduction in LTB₄ to PGE₂ ratio.
Whether these alterations are fundamental to the action of
5-ASA (or merely co- incidental to decreased inflammation
by other mechanisms) remains debatable.

There has been interest in the effects of mesalamine on
free radical production, another potential mechanism for
modulation of intestinal inflammation by these agents. 5-ASA
may act as scavengers of superoxide free radicals produced
by inflammatory cells and in some studies have shown the
ability to abrogate oxidant induced apoptosis of intestinal
epithelial cells, with positive associated effects on mucosal
barrier integrity.

Exciting recent studies have offered a more profound
insight into the precise molecular mechanisms for the anti-
inflammatory activity of 5-ASA, namely their ability to
activate peroxisome proliferators-activated receptor-gamma
(PPAR-γ). PPARs are nuclear receptors which regulate gene
expression. PPAR-γ is expressed at high levels in colonic
epithelium and appears important in maintenance of mucosal
integrity and regulation of immune activation in the intestinal
mucosa. However, PPAR activation may only be a piece of
the jigsaw and changes in the balance of angiogenic factors
in a rat model of UC have now also been elucidated. Recent
intriguing data have also highlighted a potential role for
5-ASA in altering gene expression by enteric microflora, a
novel hypothesis which could open a new avenue in our
understanding of the mechanism of action of these drugs.

Whatever the precise mechanism of action of these
agents, there is abundant evidence that they exert a significant
in vivo anti-inflammatory effect in patients with IBD. We
will proceed therefore to review this evidence with particular
focus on the efficacy of modified release mesalamine in a
therapeutic setting.

Efficacy in treatment of UC
Remission induction in UC
The therapeutic activity of delayed release mesalamine
for remission induction in UC has been observed in
placebo-controlled comparisons. An initial study involved 87 patients with mild to moderately active UC randomized to receive Asacol® 4.8 g/day, 1.6 g/day or placebo. Complete response was observed in 24% of patients receiving 4.8 g/day of mesalamine compared to 5% in the placebo group (with partial response in 50% versus 13% with placebo, P < 0.001).\textsuperscript{23} No significant difference with placebo was observed for the 1.6 g/day dose, though the numbers randomized to this arm were small (n = 11) and the comparison was likely underpowered. A subsequent multi-center trial made a placebo-controlled comparison of modified release mesalamine at two doses (2.4 g/day and 1.6 g/day) to placebo, with 158 patients with mild to moderate UC randomized. This study demonstrated significant improvement by week 6 with both doses of mesalamine (P = 0.03 for comparison with 1.6 g/day dose and P = 0.003 with 2.4 g/dose), however only at the 2.4 g/dose was a clear difference observed in the proportion of patients who showed worsening (50% in placebo group compared to 19% with mesalamine 2.4 g/day, P = 0.003).\textsuperscript{24}

Early comparative studies demonstrated that Eudragit coated mesalamine showed similar efficacy to sulfasalazine in patients with active UC but was better tolerated.\textsuperscript{25} Comparative studies followed with other 5-aminosalicylates. An initial randomized comparison of balsalazide 6.75 g/day and mesalamine 2.4 g/day in patients with active UC demonstrated higher rates of complete remission at 12 weeks with balsalazide (62% versus 37%).\textsuperscript{26} However, a subsequent larger trial of 154 patients did not detect a significant difference in remission rates at 8 weeks between patients receiving balsalazide 6.75 g/day and modified release mesalamine 2.4 g/day.\textsuperscript{27}

More recent studies of modified release mesalamine in active UC have focused on dose considerations, co-incident with development of a new 800 mg modified release tablet marketed in the United States as Asacol HD\textsuperscript{®}. Three studies have now evaluated the comparative efficacy of modified release mesalamine 2.4 g/day (dosed with a traditional 400 mg Asacol® tablet) and 4.8 g/day (dosed with the new 800 mg HD tablet). The first of these studies, ASCEND I, did not identify any overall difference in improvement at week 6 in 301 patients with mild to moderately active UC.\textsuperscript{28} However, subgroup analysis in this study suggested an advantage to the higher dose specifically for patients with moderate (as distinct from mild) disease. The second study (ASCEND II) therefore focused on this subgroup (though patients with mild disease were still recruited).\textsuperscript{29} In 268 patients randomized with moderately active disease overall improvement (defined as complete remission or clinical response) at week 6 was observed in 72% treated with mesalamine 4.8 g/day compared to 59% treated with the 2.4 g/day dose (P = 0.036). The results of a final study (ASCEND III) have recently also been reported.\textsuperscript{30} In this study 772 patients with moderately severe UC were randomized to an identical treatment regimen with remission at week 6 somewhat more common in the high dose group (43% compared to 35%, P = 0.04), although treatment success overall (the primary end-point) was not significantly different between the two groups. Interestingly, an advantage to high dose therapy was observed in the sub-group of patients previously treated for UC compared to treatment naïve/newly diagnosed patients. Table 1 summarizes the results of the principal controlled trials of the use of modified release mesalamine for remission induction in ulcerative colitis.

Remission maintenance in UC

The efficacy of modified release mesalamine for maintenance of remission has also been extensively evaluated both in comparison with placebo and in comparisons with other 5-ASA. An initial multi-center study evaluated the effectiveness of maintenance doses of mesalamine 1.6 g/day and 0.8 g/day in a placebo controlled comparison.\textsuperscript{31} 264 patients with UC in remission for 1 month were randomized with an end-point of endoscopic remission at 6 months defining treatment success. In both intention to treat and per protocol analysis mesalamine at both doses was significantly better than placebo for remission maintenance. Remission was maintained in 70.1% (1.6 g/day) and 63.3% (0.8 g/day) compared to 48.3% in the placebo group in the intention to treat analysis (P = 0.05 for comparison with 0.8 g/day dose, P = 0.005 for comparison with 1.6 g/day dose) but no significant difference between the two doses of mesalamine was detectable. A subsequent study suggested that the addition of twice weekly rectal mesalamine 4 g to maintenance oral Asacol® 1.6 g/day significantly reduced the risk or relapse at one year (from 69% with oral therapy alone to 39% with combination treatment, P = 0.036).\textsuperscript{22}

A number of studies have compared modified release mesalamine to sulfasalazine in maintenance therapy. Two early studies both showed equivalence of modified release mesalamine in remission maintenance in UC.\textsuperscript{33,34} A subsequent larger study randomized one hundred patients with a longer duration of follow up. This study demonstrated that mesalamine doses of 0.8 and 1.6 g/day were equally effective to sulfasalazine 2 to 4 g/day in remission maintenance with relapse rates at 48 weeks (primary end point) of 38 and 39% respectively.\textsuperscript{35}
A single randomized study has been reported which compared the relative efficacy of olsalazine and mesalamine. A single randomized study has been reported which compared the relative efficacy of olsalazine and mesalamine. The proportion of patients in clinical remission at 1 year was similar in both groups (66% versus 68%) with combined rates of clinical and endoscopic remission also similar. Adverse events did not differ between the two study groups. In summary, therefore, there is a significant body of evidence from randomized controlled trials of the efficacy of modified release mesalamine in both induction and maintenance of remission in UC. This agent generally appears at least as effective as other 5-ASA compounds at comparable doses. Recent developments in 5-ASA delivery technology have not enhanced its effectiveness compared to traditional 5-ASA formulations, though the possibility of once daily dosing may impact on compliance and patient preference.

### Efficacy in treatment of CD

While there is a strong general consensus about the important role of 5-ASA in general and mesalamine preparations in particular in the treatment of UC, the proper place of mesalamine in CD therapy is a much more contentious issue.

There has been only one published randomized study of the use of modified release mesalamine in treatment of active CD. Patients with mild to moderately active ileo-colonic CD were randomized to receive mesalamine 3.2 g/day (n = 20) controls in each case. The proportion of patients in clinical remission at 1 year was similar in both groups (66% versus 68%) with combined rates of clinical and endoscopic remission also similar. Adverse events did not differ between the two study groups. In summary, therefore, there is a significant body of evidence from randomized controlled trials of the efficacy of modified release mesalamine in both induction and maintenance of remission in UC. This agent generally appears at least as effective as other 5-ASA compounds at comparable doses. Recent developments in 5-ASA delivery technology have not enhanced its effectiveness compared to traditional 5-ASA formulations, though the possibility of once daily dosing may impact on compliance and patient preference.

### Table I Summary of controlled trials of modified release mesalamine for induction of remission in ulcerative colitis (UC)

| Study author | Number randomized | Treatment arm | Comparator arm | Response | Remission | Comments |
|--------------|-------------------|---------------|----------------|----------|-----------|----------|
| Schroeder23 | n = 87 | Mesalamine 4.8 g or 1.6 g for 6 weeks | Placebo | 50% (4.8 g) | 24% (4.8 g) | 4.8 g dose superior to placebo |
| Sninsky24 | n = 131 | Mesalamine 2.4 g or 1.6 g for 6 weeks | Placebo | 49% (2.4 g) | 23% (placebo) | Per protocol analysis. Both doses superior to placebo |
| Green27 | n = 101 | Mesalamine 2.4 g for up to 12 weeks | Balsalazide 6.75 g | 62% (Bal) | 37% (Mes) | ABACUS Induction Trial Balsalazide appeared superior to mesalamine |
| Levine27 | n = 154 | Mesalamine 2.4 g for 8 weeks | Balsalazide | 20% (Mes) | 19% (Bal 6.75 g) | No sig. difference noted between balsalazide 6.75 g and mesalamine 2.4 g |
| Hanauer28 | n = 301 | Mesalamine 4.8 g for 6 weeks | Mesalamine 2.4 g | 56% (4.8 g) | 35% (2.4 g) | ASCEND I includes patients with mild and moderate UC |
| Hanauer29 | n = 386 | Mesalamine 4.8 g for 6 weeks | Mesalamine 2.4 g | 72% (4.8 g) | 20% (4.8 g) | ASCEND II rates for n = 286 with moderate disease only |
| Sandborn30 | n = 772 | Mesalamine 4.8 g for 6 weeks | Mesalamine 2.4 g | 70% (4.8 g) | 43% (4.8 g) | ASCEND III only patients with moderate disease enrolled |

Abbreviations: Mes, mesalamine; Bal, balsalazide.
or placebo (n = 18). The study endpoints were remission (CDAI < 150) or response (CDAI > 150 with >70 point reduction from baseline) at 16 weeks. Complete response (remission) was observed in 45% in the treatment group compared to 22% in the placebo group where treatment failure was seen in 72% compared to 35% of the mesalamine-treated patients.

These impressive differences have not, however, been reproduced by larger studies and systematic review has failed to identify convincing evidence for the effectiveness of 5-aminosalicylates for treatment of active CD.43 Indeed a recent meta-analysis suggested that there was no evidence to support the use of 5-ASA in the maintenance of medically induced remission in CD.44 However the situation may be somewhat different with surgically induced remission in CD.45 While most of the studies evaluating the use of mesalamine in post-operative prophylaxis have made use of either prolonged release (ethyl cellulose) or Eudragit-L® coated preparations, some of the most encouraging studies have evaluated the activity of Eudragit-S® coated modified release mesalamine (Asacol®). An initial randomized study of the effect of mesalamine 2.4 g/day following first intestinal resection for CD demonstrated a dramatic difference in both the rates of endoscopic recurrence and symptomatic (clinical) recurrence at 24 months with mesalamine.46 However the study has been criticized due to the absence of an adequate placebo control with consequent concerns about bias, due to inadequate allocation concealment. A subsequent randomized placebo controlled trial by the same authors evaluated the relative efficacy of modified release mesalamine 4.0 g/day compared to 2.4 g/day when given as post-operative prophylaxis.47 The study (n = 101) did detect a reduction in the primary end-point, the number of patients with any degree of endoscopic recurrence (Rutgeerts score >0; 62% in the 4.0 g group versus 46% in the 2.4 g/day group, P < 0.04).

No significant differences were detected, however, in the rates of severe endoscopic recurrence or clinical recurrence at 12 months.

A recent meta-analysis of the effectiveness of a range of interventions for post-operative recurrence has suggested that there is evidence for a modest reduction in the risk of both clinical and endoscopic recurrence with use of mesalamine preparations when used for prevention of post-operative CD recurrence.48 The number needed to treat to prevent a single clinical recurrence is 12, which raises concerns about the cost-effectiveness of mesalamine in this context. On the other hand, it can be argued that mesalamine is safe and well tolerated, in contrast to other agents suitable for use in prevention of CD recurrence. Indeed, safety issues with mesalamine, especially those relevant to modified release formulation are what we will go on to consider next.

### Safety and tolerability in IBD

Data from controlled trials have showed that modified release mesalamine is generally well tolerated in treatment of IBD. A slight excess of gastro-intestinal side-effects such as nausea, dyspepsia and diarrhea has been reported in some placebo controlled trials (see Table 3) though without a significant dose relationship.44 However, in larger long term trials of modified release mesalamine dosed at 4.8 g/day

| Study author | Number randomized | Treatment arm | Comparator arm | Remission | Comments |
|--------------|-------------------|---------------|---------------|-----------|----------|
| Mesalamine Study Group | n = 264 | Mesalamine 1.6 g or 0.8 g for 6 months | Placebo | 70% (1.6 g) | Intention to treat analysis Both doses superior to placebo |
| Riley | n = 100 | Mesalamine 0.8–1.6 g for 48 weeks | Sulfasalazine 2–4 g | 62% (Mes) | Treatment equivalence demonstrated |
| d’Albasio | n = 69 | Mesalamine 1.6 g with twice weekly 5-ASA enema for 12 months | Mesalamine 1.6 g | 61% (combo) | Combination therapy superior to oral mesalamine alone |
| Courtney | n = 100 | Mesalamine 1.2 g for 12 months | Olsalazine 1 g | 54% (Mes) | Olsalazine superior to mesalamine |
| Green | n = 99 | Mesalamine 1.2 g for 12 months | Balsalazide 3.0 g | 58% (Mes) | Treatment equivalence demonstrated |
| Prantera | n = 331 | Mesalamine 2.4 g for 12 months | MMX 5-ASA 2.4 g | 66% (Mes) | Treatment equivalence demonstrated |

Abbreviations: Mes, mesalamine; Bal, balsalazide; SSZ, sulfasalazine; Ols, olsalazine; MMX, multimatrix formulation.
Table 3 Common adverse effects of delayed release mesalazine in a large randomized placebo controlled trial

| Adverse effect | Placebo | Mesalazine 1.6 g/day | Mesalazine 2.4 g/day |
|----------------|---------|----------------------|---------------------|
| Vomiting       | 2%      | 2%                   | 0%                  |
| Nausea         | 2%      | 2%                   | 4%                  |
| Dyspepsia      | 0%      | 0%                   | 2%                  |
| Diarrhea       | 0%      | 0%                   | 4%                  |
| Gas            | 4%      | 2%                   | 4%                  |
| Rash           | 4%      | 4%                   | 0%                  |
| Headache       | 14%     | 15%                  | 4%                  |

Recent developments in use of modified release mesalalmine

There has been increasing focus recently on the pharmaco-economic aspects of 5-ASA use in UC. Cost-effectiveness studies of 5-ASA therapies in UC have highlighted that both cost per flare prevented and cost per quality of life adjusted year (QALY) gained with maintenance 5-ASA treatment is substantial. It has even been suggested that 5-ASA maintenance may only be cost-effective in the case of sulfasalazine (where monthly drug costs are substantially lower than for other 5-ASA preparations). However, healthcare costs can vary substantially both regionally and from country to country and so the findings of such studies can be difficult to apply universally. For example a...
cost utility study performed in the UK which specifically examined the relative cost-effectiveness of high dose (HD) modified release mesalamine (4.8 g/day of Asacol HD® 800 mg) versus standard therapy with 2.4 g/day Asacol® with the standard 400 mg preparation came to a very different conclusion. This analysis favored the use of HD mesalamine as more effective, less costly and based on a cost per QALY threshold of £30,000 reported a 72% likelihood that its use was cost-effective. A specific quality of life analysis (using the IBDQ index) on patients enrolled in the ASCEND I and II studies has certainly highlighted significant early improvements in IBDQ scores with modified release mesalamine therapy.

Recent studies have also highlighted the crucial importance of non-adherence in the both the cost and utility of 5-ASA use. A recent systematic review of the impact of 5-ASA non-adherence in UC pays particular attention to the cost of associated flares. Based on data from six 5-ASA RCTs they observed relative risk of flare in excess of 3.65 in non-adherent patients. Despite the additional expenditure on medications in adherent patients, overall co-morbidity adjusted healthcare costs were greater in non-adherent individuals.

Given the high levels of non-compliance with maintenance therapy reported by UC patients, there has been significant interest in devising methods to improve adherence. Data on compliance in patients taking delayed release mesalamine have highlighted specific factors associated with non-compliance. Logistic regression revealed 3-times daily dosing (OR, 3.1; 95% CI, 1.8 to 8.4) and full-time employment (OR, 2.7; 95% CI, 1.1 to 6.9) to be independent predictors of non-compliance. Interestingly, clinical depression was the only independent predictor of complete non-compliance (OR, 10.5; 95% CI, 1.8 to 79.0), highlighting the importance of identifying and treating co-morbid mood disorders in IBD patients in order to maximize the quality of their care. Based on this data, aiming for a once or twice daily dosing regime would certainly appear worthwhile. However, while dosing frequency certainly appears important other intervention may be considered to minimize non-adherence. Physician’s time spent in education and use of other simple behavioral strategies may also constitute important adjuncts. Non-adherence is clearly an important issue in how 5-ASA drugs are used, with both significant clinical and economic consequences. Future studies of 5-ASA should ideally ensure that non-adherence is included as a key outcome component.

As well as consolidating our understanding of how best to use mesalamine in treatment of UC and possibly in CD, there may be additional novel therapeutic avenues that merit evaluation. Future studies may be useful to examine new indications for mesalamine outside of IBD therapy, including the use of modified release mesalamine in other inflammatory disorders of the colon such as diverticulitis. There has even been interest in potentially beneficial effects of the anti-inflammatory properties of mesalamine in functional bowel disorders.

**Conclusion**

Modified release mesalamine (Asacol® or Asacolon®) remains among the most popular 5-ASA formulations currently in use for the treatment of IBD. There is a significant body of data from clinical trials that modified release mesalamine is more effective than placebo for both induction and remission maintenance in UC and this agent compares favorably with other 5-ASA in comparative studies. Several recent studies have been helpful in clarifying optimal use of this agent in UC. Recent data suggest that twice daily modified release mesalamine therapy with 4.8 g/day may be more effective than 2.4 g/day in remission induction in UC patients with disease of moderate severity, although the differential effect is modest at best. Recent maintenance studies demonstrate that at equivalent doses, twice daily modified release mesalamine is as effective as once daily MMX mesalamine. The choice between these agents is likely to be determined, therefore, by factors such as cost and patient preference. It remains to be seen, however, whether once daily dosing has a clinically significant advantage over twice daily dosing with regards to long-term rates of 5-ASA compliance. There is a paucity of data to support mesalamine use in treatment of active CD or in maintenance of medically induced remission. However, there are data for a modest benefit for mesalamine in maintenance of surgically induced remission, although the number needed to treat to prevent a single clinical recurrence is approximately twelve. There are insufficient studies to determine whether any 5-ASA formulation is superior to another in this context. The real question is whether use of mesalamine is cost-effective in the post-operative setting in CD and this issue remains open for debate and further study. There are conflicting data on the cost-effectiveness of mesalamine as maintenance treatment for UC and this is an area that merits further careful evaluation. Cost-effectiveness analysis should probably also incorporate an understanding of the likely chemo preventive properties of mesalamine, as this may be an important consideration in how and why these agents are used into the future.
Disclosures
The authors disclose no conflicts of interest.

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