VIEWPOINT

Point–counterpoint: Are we overtreating patients with mild ulcerative colitis?

Akbar K. Waljee,a,b,⁎, Ryan W. Stidhamb, Peter D.R. Higginsb, Sandeep Vijana,c, Sameer D. Sainia,b

a VA Ann Arbor Health Services Research & Development Center for Clinical Management Research, Ann Arbor, MI, United States
b Division of Gastroenterology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, United States
c Division of General Medicine, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, United States

Received 18 June 2013; accepted 3 July 2013

KEYWORDS
Ulcerative colitis
Inflammatory Bowel Disease
Mesalamine
5-ASA

Clinical vignette

A 26 year-old man with a history of mild, left-sided ulcerative colitis presents to your clinic for a routine follow-up appointment. He initially presented approximately 5 years ago with intermittent rectal bleeding and diarrhea, which led to a diagnostic colonoscopy. His symptoms resolved in 1–2 weeks with a combination of oral and rectal mesalamine, and you have seen him annually since that time. At today's visit, he readily admits that he fails to take his medication on a regular basis, opting instead to use oral mesalamine as needed in response to symptoms. He estimates that he uses the medication for several weeks at a time, once or twice a year. Currently, he is having 1–2 formed bowel movements a day, with no blood and no nocturnal symptoms. His laboratory studies, including inflammatory markers and complete blood count, are normal. Upon questioning, you learn that he sees little benefit in taking a daily medication. His symptoms flare infrequently and improve quickly with initiation of mesalamine. He asks you if continuous, long-term mesalamine use confers any advantage or disadvantage over intermittent use based on symptoms, as he is currently doing.

Background

Over the last several decades, we have seen a dramatic increase in the number and variety of medications available for the treatment of inflammatory bowel disease (IBD). This increase in therapeutic options is the result of concerted and coordinated efforts by dedicated researchers, patient advocacy groups, and the pharmaceutical industry. As a result, patients with IBD now have more options for treatment than ever before. But like most chronic diseases, IBD has a wide spectrum of disease severity. For conceptual simplicity, we can dichotomize this spectrum according to whether the natural history of the disease is favorable or unfavorable. In individuals with severe disease, where the natural history is unfavorable (e.g., ulcerative pancolitis that is refractory to corticosteroids), aggressive systemic immunomodulatory treatment is often needed. High-quality care in these patients should ideally lead to resolution of symptoms, a prolonged remission, and avoidance of long-term disease complications. On the other hand, in individuals with established quiescent or mild disease, which has a favorable prognosis even without therapy, the benefits of long-term maintenance treatment are less certain.
Though it is difficult to precisely estimate the prevalence of mild disease with a favorable prognosis, these patients are common in clinical practice. Current guidelines recommend that these patients be treated with continuous 5-ASA therapy, with the goal of preventing disease flares and potentially reducing long-term complications. But complications such as colectomy or colorectal cancer (CRC) are exceedingly uncommon in this population, and available data have failed to show a clear benefit from continuous 5-ASA maintenance therapy. In this piece, we will examine the pros and cons of long-term, continuous 5-ASA use in patients with established mild UC. Because the benefits of such therapy are likely to be small, and our ability to precisely quantify these benefits is limited, we propose a more shared, informed, and individualized approach to decision-making in these patients that explicitly acknowledges these uncertainties.

**Maintenance 5-ASA therapy to prevent symptomatic relapse of disease**

**Point: Maintenance 5-ASA therapy prevents disease flares in patients with established mild UC**

UC is characterized by a wide spectrum of disease severity, with episodes of relapse and remission. Occurrence of relapse is unpredictable, and the likelihood is high. Across all degrees of UC severity, relapse rates without maintenance therapy are between 38% and 76%. Of those achieving remission with 5-ASA agents, a prospective study demonstrated that patients who were subsequently non-adherent had an approximately 5-fold greater risk of relapse, with an absolute risk reduction of approximately 40% for patients who were adherent with therapy. Admittedly, the vast majority of these patients will have resolution of symptoms with re-initiation of 5-ASA therapy. However, some non-adherent patients may also be risking escalation of disease severity. In a retrospective study, patients who had been in remission on 5-ASA therapy for at least 6 months were twice as likely to require high-dose oral or parenteral steroids when later becoming non-adherent.

**Counterpoint: Many patients perceive little clinical benefit from maintenance 5-ASA therapy**

There is little doubt that 5-ASA therapy is effective for induction and maintenance of clinical remission in mild UC. In patients who are responsive to 5-ASAs, however, the primary question is whether disease flares are frequent enough and severe enough to warrant continuous, daily medication use, particularly if such therapy is also effective when used on an as-needed basis. Though it is difficult to directly address this question, studies of 5-ASA adherence and cost–utility suggest that many patients have already decided for themselves that the answer is "no". For instance, studies examining adherence to 5-ASA medications among patients with mild UC have demonstrated that many patients (up to 60%) often fail to take their medications as prescribed. Though the reasons for non-adherence are multifactorial, a substantial proportion of non-adherent patients believe that the benefits are limited, and that these limited benefits are outweighed by the harms of inconvenient dosing regimens, large numbers of pills, and cost. The high placebo response rates reported in clinical trials (up to 77%) further support the notion that 5-ASA therapy is of limited benefit for disease maintenance in some patients with established mild disease. Finally, it is important to note that the burden of daily medication use can have an important negative effect on a patient's quality of life. A simulation model that weighed the disutility (burden) of continuous 5-ASA therapy against the frequency and severity of disease flares provided quantitative evidence for this phenomenon, with mild UC patients achieving a similar quality of life, on average, with or without 5-ASA maintenance.

**Maintenance 5-ASA therapy to reduce colectomy rates**

**Point: Maintenance of remission with 5-ASA agents is likely to reduce the rate of colectomy in mild UC**

Colectomy rates in UC range from 9% to 25% within 10 years following diagnosis, with the vast majority (approximately 90%) performed to address unremitting disease activity. Though the use of 5-ASA agents has not been shown to reduce colectomy rates, these agents have been shown to lead to variable degrees of mucosal healing. Achieving mucosal healing has been associated with lower rates of colectomy in both retrospective and prospective studies, though it should be noted that evaluating and treating for mucosal healing are not without risk and cost. Taking these data into account, it is reasonable to treat patients to potentially modify their disease course and prevent colectomy, especially when we consider the favorable safety profile of 5-ASA agents.

**Counterpoint: Maintenance of remission with 5-ASA agents is unlikely to substantially reduce the rate of colectomy in mild UC**

Many providers fear that patients who discontinue therapy will develop a disease flare that does not respond to medical therapy, ultimately requiring colectomy. Outcome data on long-term colectomy rates in patients with established mild UC are limited, but we would expect that absolute rate of colectomy in these patients to be low (meaning that the absolute benefit of therapy is also low). The strongest observational data on this topic comes from a European cohort that examined outcomes over 10 years after diagnosis among 5-ASA users and non-users. Indeed, this study found that 5-ASA medications had no significant effect on colectomy rates in patients with UC.

**Maintenance 5-ASA therapy to reduce colorectal cancer risk**

**Point: 5-ASA maintenance therapy may reduce the rate of colorectal cancer in UC patients**

Colorectal cancer (CRC) is one of the most feared outcomes in patients with long-standing UC. Historically, large population
based studies have estimated that the lifetime incidence of CRC is up to 5 times greater in UC patients than in unaffected populations.\textsuperscript{21–23} Mechanistically, there is strong evidence that chronic inflammation leads to the development of colonic dysplasia, a precursor of CRC. But population-based outcome data have failed to support the role of chronic inflammation as an important risk factor for CRC in UC.\textsuperscript{29,30} Other studies, including a recent meta-analysis, have called into question the chemopreventive effects of 5-ASA agents.\textsuperscript{31–33} Thus, the theoretical benefits of chemoprevention for CRC in UC are not borne out by the sum of available outcome data.

Counterpoint: 5-ASA maintenance therapy does not reduce the rate of colorectal cancer in UC patients

Prior studies demonstrated that chronic colonic inflammation is associated with the development of colonic dysplasia, a precursor of CRC. But population-based outcome data have failed to support the role of chronic inflammation as an important risk factor for CRC in UC.\textsuperscript{29,30} Other studies, including a recent meta-analysis, have called into question the chemopreventive effects of 5-ASA agents.\textsuperscript{31–33} Thus, the theoretical benefits of chemoprevention for CRC in UC are not borne out by the sum of available outcome data.

Discussion

5-ASA agents have long been the mainstay of treatment in patients with mild UC. Though these agents are less potent than other available therapies for UC, they have a favorable side-effect profile, leading to their widespread use. The potential benefits of 5-ASA agents include: (1) symptom control,\textsuperscript{34,35} and associated improvements in quality of life and health care utilization; (2) reduction in colectomy rates; and, (3) reduction in CRC incidence. However, the absolute benefit of any intervention is dependent on the baseline risk of the condition. In individuals with mild UC, a prevalent patient population with a favorable long-term prognosis, the absolute risk of CRC and colectomy is low. Therefore, the long-term benefits of therapy are small at best and deserve to be weighted against the potential clinical and economic harms.

We propose that the decision of whether or not to treat patients with established mild UC is more complex than the treatment decision in individuals who have more severe disease (in whom the benefits clearly outweigh the harms). Braddock et al. have defined complex decisions as those in which the effect on the patient is extensive, the medical consensus is controversial, and the outcomes are uncertain.\textsuperscript{34} In mild UC treated with 5-ASA therapy, the patient is asked to take daily medication, often at significant cost, for a small benefit. There is reasonable consensus that daily use of 5-ASA agents can reduce the risk of flares. However, there is also evidence that on-demand use of 5-ASA may be an effective strategy, decreasing the marginal benefits of daily medication use.\textsuperscript{36} Arguments that daily 5-ASA use may be effective in reducing the risk of more feared UC outcomes such as colectomy and CRC risk are largely theoretical and are not consistently supported by existing (though limited) data. While there is substantial uncertainty about the exact magnitude of the benefit of 5-ASA therapy, the sum of available evidence suggests that the overall benefit is likely to be small.

On the other hand, there is a small but real potential for harm (renal injury, and in some instances, end-stage renal disease).\textsuperscript{37–39} and there is a daily burden and cost to taking medication. It is clear that for many patients, daily medication is viewed as being of relatively little benefit, as patients who achieve remission in the short-term often fail to adhere to their medication in the long-term. While this non-adherence is certainly multifactorial, there is reasonable evidence that some patients perceive little benefit to continuous medication use in a low-risk setting.

Based on the evidence outlined above, we believe that patients warrant a shared, informed approach to decision-making about chronic therapy for mild UC.\textsuperscript{40} Current guidelines suggest a relatively one-size fits all approach — namely that nearly all patients with mild UC take daily 5-ASA medications. Instead, a shared approach to decision-making considers both potential benefits and potential clinical and economic harms on a case-by-case basis, allowing doctor and patient to make the best decision for a given individual.

One widely endorsed approach to complex decision-making is the use of decision aids, interventions that help individuals explicitly consider the pros and cons of treatment in order to improve informed decision-making. High-quality decision aids educate patients on the decision context and present tailored risk and benefit information in various ways. They also help patients more explicitly weigh the factors that are important in making an informed decision. Decision aids have been used in a variety of healthcare contexts, including treatment for IBD.\textsuperscript{41} Studies of decision aids for IBD have shown that they are effective in educating patients and, in some instances may influence decision-making behavior.\textsuperscript{42,43} However, prior work on decision aids in IBD has focused primarily on high-risk patients who have an unfavorable prognosis and are making a choice between treatment strategies with varying degrees of toxicity. We believe that such an approach is also needed in patients with established, mild UC, a prevalent population in whom the benefits of long-term 5-ASA therapy are small or uncertain.

Though a more informed approach to decision-making is needed in this patient population, we must also contend with gaps in our understanding of established mild UC. For instance, we have limited data on the absolute long-term prognosis in terms of colectomy and CRC. We also have no direct data to support or refute the notion that disease activity may accelerate in these patients if untreated, requiring more aggressive therapies. Finally, we have insufficient quantitative data on the optimal balance between the benefits and risks of 5-ASA therapy. Prior work in this area has largely ignored the renal risks of long-term 5-ASA therapy, a clinical harm that could have important consequences.\textsuperscript{37–39}

Of course, the uncertainty that currently exists in the literature on this topic does not preclude efforts to develop decision aids to more systematically inform patients about the potential benefits, harms, and uncertainty associated with use of these medications.
Clinical vignette

You explain to your patient that continuous, long-term mesalamine use has several potential benefits, but the supporting data are limited. For symptom control, studies suggest that, on average, remission is more likely in patients who use mesalamine regularly. On the other hand, there is less data to suggest that treating on demand is less efficacious. Furthermore, the data on long-term benefits in terms of colectomy rate and CRC risk are also controversial. The risks of the medication are small, but renal toxicity is possible. It is important that renal function be monitored periodically to assess for the interval development of renal injury. Finally, if cost is an issue, lower cost alternatives (such as sulfasalazine or balsalazide) could be considered. The patient appreciates your honesty and time in explaining these issues. He decides to begin taking mesalamine more regularly, primarily due to concern for CRC. He tells you that his friend, who also suffered from UC, recently developed CRC unexpectedly.

Conflict of interest

None.

References


43. Siegel CA, Marden SN. Crohn’s disease patients report their definitions of "rare" adverse event, remission and the importance of mucosal healing: a quantitative and qualitative study of what patients really think. *Gastroenterology* 2011;140:5:141.