Journal of Crohn's and Colitis (2014) 8, 80–84

Available online at www.sciencedirect.com

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VIEWPOINT

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

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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.

☆ Grant support: Dr. Saini's and Dr. Waljee's research is funded by a VA HSR&D CDA-2 Career Development Award. Dr. Stidham's research is funded through the Crohn's and Colitis Foundation of America Career Development Award.

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1873-9946/$ - see front matter. Published by Elsevier B.V. on behalf of European Crohn's and Colitis Organisation.
http://dx.doi.org/10.1016/j.crohns.2013.07.003

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.[1,2] But complications such as colectomy or colorectal cancer (CRC) are exceedingly uncommon in this population, and (as detailed below) 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%.[3] 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.[4] 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.[5]

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.[6,7] 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.[4,8] 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.[9,10] 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.[11–13] 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.[14]

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,[15] with the vast majority (approximately 90%) performed to address unremitting disease activity.[16] 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.[17] Achieving mucosal healing has been associated with lower rates of colectomy in both retrospective and prospective studies,[18,19] 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.[20]

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