Mesalamine for the prevention of recurrent diverticulitis?

Recurrent diverticulitis represents a relevant clinical problem, involving up to a quarter of patients after the first episode of diverticulitis. Unfortunately, there are no evidence-based data that indicate a targeted therapeutic approach for the prevention of recurrent diverticulitis.

During the last years, based on the hypothesis that mucosal inflammation could act as a trigger for acute diverticulitis and its recurrence, the use of mesalamine [5-aminosalicylic acid (5-ASA)], has been considered as a possible pharmacological agent for prevention of this condition.

In this commentary, we undertake a critical analysis of a Cochrane review by Carter F published 3 years ago aimed to evaluate the efficacy of 5-ASA for the prevention of recurrent diverticulitis (primary outcome) and the adverse effect of therapy (secondary outcome).

Firstly, we identified some concerns in the research review methods:

- inclusion of trials using colonoscopy to diagnose diverticulitis. In patients with diverticulitis, colonoscopy is burdened by a higher perforation rate and no data supporting its use are available, making this diagnostic method very questionable in this setting;
- use rectal administration of 5-ASA for a condition that does not, by definition, affect the rectum, with the length of involvement of sigmoid that can be variable and unpredictable.

The authors, included 7 randomized controlled trials (RCTs) with a total of 1805 participants. Regarding the primary endpoint, 5-ASA was not superior to control intervention for the prevention of diverticulitis (RR 0.69; 95% CI 0.43–1.09) with a very low quality of evidence.

The most relevant point is the high heterogeneity of the included studies (I^2 = 79%), mainly regarding: control regimens, 5-ASA dosage, participants' age and gender, and number of prior episode of diverticulitis.

Other critical methodological issues are the diagnostic method for the index and recurrent episode of diverticulitis (computed tomography (CT) scan/ ultrasonography *vs* other methods), and risk of bias (unclear *vs* high risk of bias).

Taking into account the high heterogeneity of the studies, the most interesting results are those related to the subgroup analysis, particularly regarding control regimen and method of diagnosis:

- in the studies comparing the efficacy of 5-ASA versus placebo, no efficacy of 5-ASA for recurrence prevention was found;
- in the studies considering the consistent (CT or ultrasonography) *vs* non-consistent methods (clinical assessment, laboratory and colonoscopy) to diagnose diverticulitis, no significant treatment effect was found (RR 1.11, 95% CI 0.80–1.35). Remarkably, in the

only 3 trials employing CT scan for the diagnosis of primary diverticulitis and recurrence no significant treatment effect was found (RR 1.07, 95% CI 0.81–1.40).

The secondary outcome was to evaluate adverse effects of therapy: authors analysed 5 out of 7 trials, reporting that frequency of adverse effects is similar between 5-ASA and controls (RR 0.98, 95% CI 0.91–1.06), without heterogeneity among studies ($I^2 = 0$) and with moderate quality evidence.

More recently, 2 large phase-3, randomized placebo-controlled double-blind trials by Kruis W et al (Aliment Pharmacol Ther 2017;46:282–291), randomized patients with prior diverticulitis (CT/ultrasonography- proven) to receive 3-g 5-ASA daily or placebo (SAG-37) or 1.5-g, 3-g mesalazine or placebo for 96 weeks (SAG-31), founding that 5-ASA was not superior to placebo in preventing diverticulitis recurrence.

Actually, even if no robust data is available to support use of 5-ASA in this setting, this is one of the most frequently prescribed drugs in patients with clinical history of recurrent diverticulitis, highlighting the gap between real-life clinical practice and an evidence-based approach (Cremon C et al, 2019; United Eur Gastroenterol J; 7:815–824).

In conclusion, the effects of 5-ASA on recurrence of diverticulitis are uncertain, and its use is currently not supported. Further RCTs are needed to evaluate a targeted therapeutic approach in this setting.

Marilia Carabotti, Francesca Falangone, Bruno Annibale
Medical-Surgical Department of Clinical Sciences and Translational Medicine, University Hospital Sant'Andrea, University Sapienza, Rome, Italy

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