European Review for Medical and Pharmacological Sciences 2013; 17: 3244-3248

Intermittent versus every-day mesalazine therapy in preventing complications of diverticular disease: a long-term follow-up study

A. TURSI[1], F. DI MARIO[2], G. BRANDIMARTE[3], W. ELISEI[4], M. PICCHIO[5], S. LOPERFIDO[2], N. DAL BO'[2], F. FERRARA[2], R. MARCELLO[2], H. HERAS SALVAT[2], C. SCARPIGNATO[6]

[1]Gastroenterology Service, ASL BAT, Andria (Barletta), Italy
[2]Gastroenterology Unit, "Cà Foncello" Hospital, Treviso, Italy
[3]Department of Internal Medicine, Division of Gastroenterology, "Cristo Re" Hospital, Rome, Italy
[4]Division of Gastroenterology , ASL RMH, Albano Laziale, Rome, Italy
[5]Division of Surgery, "P. Colombo" Hospital, ASL RMH, Velletri, Rome, Italy
[6]Department of Anatomy, Pharmacology & Forensic Sciences, Laboratory of Clinical Pharmacology, University of Parma, Parma, Italy

Abstract. – BACKGROUND: Mesalazine seems to be effective in preventing recurrence of acute uncomplicated diverticulitis (AUD), but the optimal mesalazine scheme to achieve these results is still debated.

AIM: To assess the effectiveness of two different mesalazine-based treatments in preventing recurrence of AUD and the occurrence of other complications of diverticular disease (DD) during a long-term follow-up.

PATIENTS AND METHODS: We reviewed 311 patients suffer from recent episode of AUD and undergoing to mesalazine treatment: 207 (group A, 105 males, median age 63 years, range 47-74 years) were treated with mesalazine 1.6 g for 10 days each month, whilst 104 (group B, 55 males, median age 65 years, range 50-72 years) were treated with mesalazine 1.6 g every day. Patients were followed-up every 6 months (median 7.5 months, range 5-13 months).

RESULTS: Patients were followed-up for a mean time of 3 years (range 12-72 months). Overall, occurrence of complication recurred more frequently in group A than in group B ($p = 0.030$, log-rank test). Acute diverticulitis recurred in 17 (8.2%) patients in group A and in 3 (2.9%) in group B; diverticular bleeding occurred in 4 (1.9%) patients in group A and in 1 (0.96%) patient in group B; surgery was required in 3 (1.4%) patients in group A and in no (0%) patient in group B.

CONCLUSIONS: This is the first study showing that long-term mesalazine treatment is significantly better that intermittent mesalazine treatment in preventing occurrence of DD complications after an attack of acute diverticulitis.

Key Words:
Acute uncomplicated diverticulitis, Complications, Follow-up, Mesalazine, Recurrence.

Introduction

Diverticular disease (DD) of the colon is common in westernized societies, and its prevalence increases with age. Diverticulosis affects about two-thirds of the elderly, and a large majority of those affected will remain entirely asymptomatic. Nonetheless, an estimated 20-25% of patients may manifest clinical illness: the so-called "Diverticular Disease"[1].

The most important complication of DD is represented by acute diverticulitis[2]. It may be subdivided into uncomplicated diverticulitis, characterized by acute inflammation of the diverticula without complications, and complicated diverticulitis, characterized by acute diverticular inflammation associated to complications (abscesses, fistulas, stenoses)[3]. Acute diverticulitis may also recur, and the long-term recurrence rate of diverticulitis is up to 20%[4-6]. Although recurrence of diverticulitis is common, there is little evidence to define the optimal approach to managing diverticulitis after an acute episode.

Although antibiotics are the mainstay for the treatment of diverticulitis[7], their use in preventing diverticulitis recurrence seems to be not effective[8-10]. Mesalazine has been recently identified as a promising therapeutic option in the treatment of symptomatic, uncomplicated diverticular disease[11,12]. Moreover, mesalazine has been suggested as a promising tool in preventing diverticulitis recurrence[13]. Despite the increasing number of studies, there are no clear data about the optimal mesalazine dosage to maintain remission after an attack of Acute Uncomplicated Diverticulitis (AUD)[14].

Corresponding Author: Antonio Tursi, MD; e-mail: antotursi@tiscali.it

The aim of the present study was, therefore, to investigate the outcome of two different therapeutic approaches based on mesalazine (daily or cyclic treatment) in order to prevent recurrence of diverticulitis and the occurrence of other DD complications after an attack of AUD.

Patients and Methods

We retrospectively reviewed patients undergoing to diagnosis of AUD in four Gastroenterological Centres (one located in north, two in centre and one in south Italy). From January 2001 to January 2011, 523 patients underwent to diagnosis of AUD (319 males, 204 females, mean age 64 years, range 40-85 years).

Diagnosis of AUD was made according to radiological criteria: thickening of the colon harbouring diverticula, with fat stranding and without complications (namely perforation, abscesses, and fistulas), assessed by Computerized Tomography (CT) scan[3,7], and associated to increased values of inflammatory indexes (white blood cell count and/or erythrocyte sedimentation rate and/or C-reactive protein).

All patients were treated with mesalazine 3.2 g/day, rifaximin 800 mg/day, and metronidazole 1 g/day for 7 days to obtain remission. Two hundred and sixty-seven patients (85.85%) obtained remission, whilst 44 patients (14.15%) required further therapy with intravenous treatment with third generation cephalosporin to obtain remission.

All patients underwent clinical remission, defined as disappearance of abdominal symptoms (absence of abdominal pain, regular bowel habits) and return to normal values of inflammatory indexes. None of them required surgery at that time.

Two weeks after obtaining remission, patients underwent to colonoscopy in order to confirm diverticulosis and to exclude other colonic disease.

Exclusion criteria for our research were: lacking of information about the clinical appearance, and/or natural history, and/or treatment of the disease; solitary diverticulum of the colon; previous colonic surgery; concomitant colonic or extra colonic cancer; diagnosis of Inflammatory Bowel Diseases or Segmental Colitis Associated with Diverticulosis; prescription of cyclic antibiotic treatment at hospital discharging; chronic hematological or hepatic or renal diseases; immunodeficiency; pregnancy, or lactation; proven intolerance to mesalazine. According to these excluding criteria, 212 patients were excluded from the final evaluation.

About the 311 patients meeting the study criteria, we identified two different groups taking mesalazine in different fashion: 207 patients (group A, 105 males, mean age 63 years, range 47-74 years) were treated with mesalazine 1.6 g/day for 10 days months; 104 patients (group B, 55 males, mean age 65 years, range 50-72 years) were treated with mesalazine 1.6 g every day.

In group A, 20 patients (9.66%) suffered from three episodes, 22 patients (10.63%) suffered from two, and 165 patients (79.71%) suffered from one episode of diverticulitis respectively.

Patients were re-evaluated every 6 months (range 5-13 months, median 7,5 months) lasting the follow up.

In group B, 6 patients (5.76%) suffered from three episodes, 11 patients (10.57%) suffered from two, and 87 patients (83.65%) suffered from one episode of diverticulitis respectively.

Patients were re-evaluated every 6 months (range 5-13 months, median 7,5 months) lasting the follow up in order to identify: recurrence of diverticulitis; diverticular bleeding; needs of surgery due to recurrence of the disease.

Statistical Analysis

The collection and analysis of data were performed by using Medacalc® version 7.3 (Frank Schoonjanas, Broekstraat, Belgium). Statistical analysis was performed by Kaplan Meier method and groups were compared with the log rank test. Pearson χ^2 test was used for categorical data. $p < 0.05$ was considered significant.

Results

Patients were followed-up for a mean time of 3 years (range 12-72 months). The two groups of patients did not differ in age (group A, mean age 63 years, range 47-74 years; group B, mean age 65 years, range 50-72 years; $p = 0.1$), gender (group A, 105 males vs. group B, 55 males $p = 0.1$), and consumption of medication.

Overall, occurrence of complications recurred more frequently in group A than in group B, as also shown in Figure 1 with the Kaplan-Maier analysis (log rank test: $p = 0.03$).

In particular, AUD recurred in 17 (8.2%) patients in group A and in 3 (2.9%) in group B. Diverticular bleeding occurred in 4 (1.9%) patients in group A and in 1 (0.96%) patient in group B. Finally, surgery was required in 3 (1.4%) patients

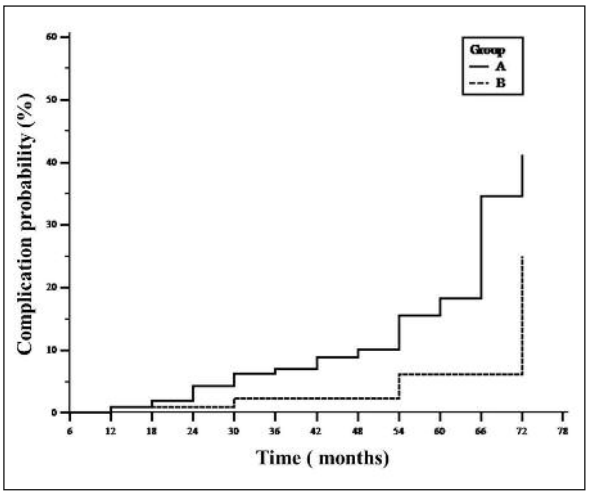

Figure 1. Kaplan-Maier curves of complication probability during the follow-up in the two study groups (Log-rank test, $p = 0.030$).

in group A (two patients for developing of complicated diverticulitis and one patients due colonic stenosis) and in no (0%) patient in group B.

Twelve group A and 3 group B patients died during the follow-up, but not any of these deaths was related to DD: 11 died from cardiovascular disease (myocardial infarction, stroke, aortic aneurysm rupture) and cancer occurred in four patients (1 lung cancer, 1 prostate cancer, 1 breast cancer, and 1 gastric cancer).

Discussion

Diverticulitis represents a significant economic and clinical burden to the western Health Care Systems and its patients[15]. Recent studies take a lot of care in identifying the best therapeutic strategy in preventing diverticulitis recurrence. We know that it occurs frequently. A large, long-term follow-up study on patients who were initially hospitalized for acute diverticulitis and subsequently included in a follow-up, found that 19% of patients underwent emergent colectomy, and 13% had at least one recurrence during a 9 year mean follow-up[15]. Similar results were described by a larger study[16]. Moreover, recent studies reported that recurrence rate of diverticulitis is 19-54% at 5 year follow-up[4,5,17]. These data suggest that an optimal therapeutic strategy is needed in order to prevent diverticulitis recurrence and its complications. Unfortunately, no data are currently available about this specific problem.

In Italy, it is very popular an antibiotic-based strategy, based on a monthly cyclic treatment with rifaximin, a broad spectrum non-absorbable antibiotic, in preventing recurrence of diverticular disease and diverticulitis[8]. However, recent systematic reviews criticize this approach, because of the high costs for National Health System and the lack of definitive results in preventing diverticulitis[8,9]. In fact the only placebo-controlled study did not rifaximin better than placebo in preventing diverticulitis occurrence[18]. A very recent study found rifaximin more effective than fibre in preventing diverticulitis recurrence[19]. However, the open-label design limit the importance of these results.

A different therapeutic approach in diverticular disease, based on mesalazine, has been investigated recently. Some studies showed that mesalazine (alone or in combination with antibiotics) seems a promising tool in treating and preventing recurrence of this disease[14]. In particular, a recent double-blind, placebo controlled study found mesalazine (alone or in combination with antibiotics), effective in maintain remission in patients suffer from Symptomatic Uncomplicated diverticular disease (SUDD) and in preventing diverticulitis occurrence[12]. Finally, we recently found that mesalazine is better than rifaximin in preventing diverticulitis recurrence in an head-to-head open-label trial[20]. This because the mechanisms that underlie the development of inflammation in diverticulitis may be similar to those that drive the inflammation in inflammatory bowel disease (IBD). Deficiency in dietary fiber consumption in patients with diverticulitis is associated with changes in microflora, which in turn may induce low-grade inflammation. This would cause an increased production of pro-inflammatory cytokines and decreased production of anti-inflammatory cytokines[21-23]. Thus, using mesalazine seems to be a promising therapeutic tool in this way, despite the results coming from the first placebo-controlled studies are still debated[24-26].

We found that mesalazine taken daily is better than intermittent mesalazine treatment in preventing all type of DD complication after an attack of AUD. These results seem to be different to that obtained in preventing SUDD recurrence, where a 10-day/month intermittent mesalazine treatment seems to be better than placebo in preventing recurrence of the disease[12]. This finding may be explained by different effectiveness in controlling inflammation. We know that persis-

tence of endoscopic and histological inflammation are risk factor for diverticulitis recurrence[27]. After resolution of acute inflammation, mesalazine taken daily seems to be, therefore, more able in controlling inflammation to control inflammation, similar to what occur in IBD. This mechanism may also explain the results of some recent placebo-controlled trials. Stollman et al[24] found a short-lasting (3 months) mesalazine course not superior than placebo in preventing recurrence of the disease. Parente et al[25] found a 10-day/month intermittent mesalazine treatment wasn't better than placebo in preventing diverticulitis recurrence. On the contrary, Gaman et al[26] found a long-lasting daily mesalazine course better than placebo in preventing recurrence of the disease and occurrence of DD complications. Long-lasting daily mesalazine course seems, therefore, the best mesalazine-based therapeutic approach in preventing occurrence of DD complication.

Conclusions

This study was an open fashion and retrospective, not randomized trial. However, it is undoubtful that the results of this work are interesting for clinical practice. We found for the first time that long-term daily treatment with mesalazine seems to be a valid therapeutic strategy in preventing recurrence of diverticulitis and in preventing occurrence of other DD complications, thanks to its effect in controlling persistence of inflammation after an attack of AUD. These findings are surprising similar to what occur in IBD, and lead to consider diverticulitis as a chronic disease requiring long-term daily anti-inflammatory treatment in order to prevent recurrence and complications.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Sheth AA, Longo W, Floch MH. Diverticular disease and diverticulitis. Am J Gastroenterol 2008; 103: 1550-1556.
2) Tursi A. New physiopathological and therapeutic approaches to diverticular disease of the colon. Expert Opin Pharmacother 2007; 8: 299-307.
3) Tursi A, Brandimarte G, Giorgetti G, Elisei W, Maiorano M, Aiello F. The clinical picture of uncomplicated versus complicated diverticulitis of the colon. Dig Dis Sci 2008; 53: 2474-2479.
4) Broderick-Villa G, Burchette RJ, Collins JC, Abbas MA, Haigh PI. Hospitalization for acute diverticulitis does not mandate routine elective colectomy. Arch Surg 2005; 140: 576-581.
5) Anaya DA, Flum DR. Risk of emergency colectomy and colostomy in patients with diverticular disease. Arch Surg 2005; 140: 681-685.
6) Binda GA, Arezzo A, Serventi A, Bonelli L; Italian Study Group on Complicated Diverticulosis (GISDIC). Multicentre observational study of the natural history of left-sided acute diverticulitis. Br J Surg 2012; 99: 276-285
7) Tursi A, Papagrigoriadis S. Review article: the current and evolving treatment of colonic diverticular disease. Aliment Pharmacol Ther 2009; 30: 532-546.
8) Tursi A. Diverticular disease: what is the best long-term treatment? Nat Rev Gastroenterol Hepatol 2010; 7: 77-78.
9) Zullo A, Hassan C, Maconi G, Manes G, Tammaro G, De Francesco V, Annibale B, Ficano L, Buri L, Gatto G, Lorenzetti R, Campo SM, Ierardi E, Pace F, Morini S. Cyclic antibiotic therapy for diverticular disease: a critical reappraisal. J Gastrointestin Liver Dis 2010; 19: 295-302.
10) Maconi G, Barbara G, Bosetti C, Cuomo R, Annibale B. Treatment of diverticular disease of the colon and prevention of acute diverticulitis: a systematic review. Dis Colon Rectum 2011; 54: 1326-1338.
11) Di Mario F, Aragona G, Leandro G, Comparato G, Fanigliulo L, Cavallaro LG, Cavestro GM, Iori V, Maino M, Moussa AM, Gnocchi A, Mazzocchi G, Franzé A. Efficacy of mesalazine in the treatment of symptomatic diverticular disease. Dig Dis Sci 2005; 50: 581-586.
12) Tursi A, Brandimarte G, Elisei W, Giorgetti GM, , Forti G, Rodinò S, Saccà N, D'Amico T, Portincasa P, Capezzuto E, Spadaccini A, Fiorella S, Polimeni N, Picchio M, Danese S. Mesalazine and/or Lactobacilllus casei in maintaining remission of symptomatic uncomplicated diverticular disease of the colon: a randomised, double-blind, placebo-controlled study. Gut 2012; 61 (Suppl. 3): A101-102.
13) Tursi A, Brandimarte G, Daffinà R. Long-term treatment with mesalazine and rifaximin versus rifaximin alone for patients with recurrent attacks of acute diverticulitis of colon. Dig Liver Dis 2002; 34: 510-515.
14) Tursi A, Joseph RE, Streck P. Expanding applications: the potential usage of 5-aminosalicylic acid in diverticular disease. Dig Dis Sci 2011; 56: 3112-3121.
15) Sandler RS, Everhart JE, Donowitz M, Adams E, Cronin K, Goodman C, Gemmen E, Shah S, Avdic A, Rubin R. The burden of selected digestive diseases in the United States. Gastroenterology 2002; 122: 1500-1511.

16) Ruffolo C, Scarpa M, Faggian D, Basso D, D'Incà R, Plebani M, Sturniolo GC, Bassi N, Angriman I. Subclinical intestinal inflammation in patients with Crohn's disease following bowel resection: a smoldering fire. J Gastrointest Surg 2010; 14: 24-31.

17) Käser SA, Fankhauser G, Glauser PM, Toia D, Maurer CA. Diagnostic value of inflammation markers in predicting perforation in acute sigmoid diverticulitis. World J Surg 2010; 34: 2717-2722.

18) Papi C, Ciaco A, Koch M, Capurso L. Efficacy of rifaximin in the treatment of symptomatic diverticular disease of the colon. A multicentre double-blind placebo-controlled trial. Aliment Pharmacol Ther 1995; 9: 33-39.

19) Lanas A, Ponce J, Bignamini A, Mearin F. One year intermittent rifaximin plus fibre supplementation vs. fibre supplementation alone to prevent diverticulitis recurrence: a proof-of-concept study. Dig Liver Dis 2013; 45: 104-109.

20) Tursi A, Elisei W, Giorgetti GM, Inchingolo CD, Nenna R, Picchio M, Maiorano M, Penna A, Lecca PG, Brandimarte G. Effectiveness of different therapeutic strategies in preventing diverticulitis recurrence. Eur Rev Med Pharmacol Sci 2013; 17: 342-348.

21) Tursi A, Elisei W, Brandimarte G, Giorgetti GM, Inchingolo CD, Nenna R, Picchio M, Giorgio F, Ierardi E. Musosal tumour necrosis factor in diverticular disease of the colon is overexpressed with disease severity. Colorectal Dis 2012; 14: e258-263.

22) Humes DJ, Simpson J, Smith J, Sutton P, Zaitoun A, Bush D, Bennett A, Scholefield JH, Spiller RC. Visceral hypersensitivity in symptomatic diverticular disease and the role of neuropeptides and low grade inflammation. Neurogastroenterol Motil 2012; 24: 318-e163

23) Tursi A, Elisei W, Brandimarte G, Inchingolo CD, Nenna R, Picchio M, Giorgio F, Ierardi E. Mucosal expression of basic fibroblastic growth factor, Syndecan 1 and tumor necrosis factor-alpha in diverticular disease of the colon: a case-control study. Neurogastroenterol Motil 2012; 24: 836-e396

24) Stollman N, Magowan S, Shanahn F, Quigley E. Efficacy of delayed-release mesalamine in the prevention of GI symptoms following acute diverticulitis: results of the DIVA trial. Am J Gastroenterol 2010; 105(Suppl 1): S139.

25) Parente F, Bargiggia S, Prada A, Bortoli A, Giacosa A, Monti C, Germanà B, Galliani E, Ferrari A, Secreto P, Casella G, Miori G, De Pretis G. Randomised multicentre pilot double-blind placebo-controlled study evaluating the efficacy and safety of mesalazine in the prevention of recurrence of diverticulitis: interim analysis after 24-month follow-up. Dig Liver Dis 2011; 43S: S135.

26) Gaman A. Teodorescu R, Georhescu EF, Abagiu MT. Prophylactic effects of mesalamine in diverticular disease. Falk Symposium 2011; 178: Abstract 13.

27) Tursi A, Elisei W, Giorgetti GM, Lecca PG, Papa A, Brandimarte G. Persistence of endoscopic and histological inflammation are risk factors of diverticulitis recurrence after attack of acute uncomplicated diverticulitis. Gastroenterology 2011; 140(5, Suppl. 1): S-61.