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 occurred 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 diverticulitis2. 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 diverticulitis7, their use in preventing diverticulitis recurrence seems to be not effective8-10. Mesalazine has been recently identified as a promising therapeutic option in the treatment of symptomatic, uncomplicated diverticular disease11,12. Moreover, mesalazine has been suggested as a promising tool in preventing diverticulitis recurrence13. 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.
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 erythrocytesedimentation 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\textsuperscript{\textregistered} 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 $\chi^2$ 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 (0.9%) patient in group B. Finally, surgery was required in 3 (1.4%) patients.
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 diverticulardisease, 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 maintaining remission in patients suffering 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-
Interventions of endoscopic and histological inflammation are risk factors for diverticulitis recurrence. After resolution of acute inflammation, mesalazine taken daily seems to be, therefore, more able in controlling inflammation to control complications, similar to what occurs in IBD. This mechanism may also explain the results of some recent placebo-controlled trials. Stollman et al. found a short-lasting (3 months) mesalazine course not superior than placebo in preventing recurrence of the disease. Parente et al. found a 10-day/month intermittent mesalazine treatment wasn't better than placebo in preventing diverticulitis recurrence. On the contrary, Gaman et al. 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 complications.

**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**


