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Effectiveness of different therapeutic strategies in preventing diverticulitis recurrence

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Abstract. – BACKGROUND: Colonic diverticulitis shows a high recurrence rate.

AIMS: To assess the efficacy of three different therapeutic strategies in preventing diverticulitis recurrence.

MATERIALS AND METHODS: One hundred thirty patients suffering from Acute Uncomplicated Diverticulitis (AUD) (81 males, 49 females, mean age 64.71 years, range 40-85) were prospectively assessed. After obtaining remission, considered present when both endoscopic and histological damage were absent, the patients were treated with mesalazine 1.6 g/day (59 patients, group A), or rifaximin 800 mg/day for 7 days every month (52 patients, group B). Clinical, endoscopic and histological follow-up was performed after 6, 12 and thereafter every 12 months after diagnosis of AUD.

RESULTS: Seven patients were excluded from final evaluation because they were lost to follow-up. Fifty-five group A patients and 49 group B patients patients were available for the final assessment at the end of a 24-month follow-up. Sustained remission was significantly higher in group A with respect to group B.

CONCLUSIONS: Patients taking mesalazine have lower risk of diverticulitis recurrence than patients taking rifaximin because of the lower prevalence of persisting endoscopic and histological inflammation.

Key Words:
Acute uncomplicated diverticulitis, Endoscopy, Follow-up, Histology, Mesalazine, Recurrence, Rifaximin.

Introduction

Diverticular disease 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 diverticular disease 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]. Antibiotics are currently used in the treatment of uncomplicated disease[4], but mesalazine has been recently identified as a promising therapeutic option in the treatment of symptomatic, uncomplicated diverticular disease[5,6]. Despite the increasing number of studies, there are no clear data about the optimal treatment to maintain remission after an attack of Acute Uncomplicated Diverticulitis (AUD). It is considered that bacterial overgrowth, aided by fecal stasis within diverticula, may have a role not only in determining abdominal symptoms, such as bloating and discomfort, but also in determining recurrence of the disease[4]. Unabsorbed antibiotics may, therefore, reduce both the severity of symptoms both the risk of complications related to bacterial overgrowth[4]. Rifaximin, a broad-spectrum nonabsorbable antibiotic, has been, therefore, investigated in this way. However, its use in preventing recurrence of diverticulitis seems to be inconclusive[7-9]. It is also well know that the mechanisms that underlie the development of inflammation in

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diverticulitis may be similar to those that drive the inflammation in inflammatory bowel diseases (IBD)[4]. Deficiency in dietary fiber consumption in patients with diverticulitis is associated with changes in the colonic microflora, which in turn may induce low-grade inflammation. This would cause an increased production of pro-inflammatory cytokines and decreased production of antiinflammatory cytokines[4]. Thus, using mesalazine seems to be a promising therapeutic tool in this way[4].

The aim of the present study was to investigate the outcome of two different therapeutic approaches (mesalazine or rifaximin) in maintaining remission and in preventing recurrence of the disease.

Materials and Methods

From January 2004 to June 2009, 130 patients underwent diagnosis of AUD (81 males, 49 females, mean age 64.71 years, range 40-85). Diverticular disease was diagnosed for the first time in 93 patients, whilst 37 patients referred history of diverticular disease.

Diagnosis of AUD was made according to endoscopic and radiological criteria: macroscopic and microscopic inflammation involving the colon harbouring diverticula, and affecting bowel wall without complications (namely perforation, abscesses, and fistulas), assessed by Computerized Tomography (CT) scan[3,7]. All patients underwent colonoscopy and abdominal CT.

AUD was diagnosed by abdominal CT scan first in 73 patients. In those patients, abdominal CT scan was performed due to acute abdominal pain at admittance to the Emergency Department. Colonoscopy was performed in those patients at least 7 days after exclusion of complicated acute diverticulitis on CT scan.

AUD was diagnosed by colonoscopy first in 57 patients. In those patients, endoscopy was performed as outpatients because of abdominal symptoms, mainly due to history of abdominal pain and/or constipation or diarrhea. Abdominal CT was performed immediately after colonoscopy.

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. One hundred and seven patients (82.31%) obtained remission, whilst 23 patients (17.69%) required further therapy with intravenous treatment with third generation cephalosporin to obtain remission. All patients underwent clinical remission, defined as disappearance of abdominal symptom (absence of abdominal pain, regular bowel habits) and return to normal values of inflammatory indexes (erythrocyte sedimentation rate, C-reactive protein, white blood cell count, fecal calprotectin). None of them required surgery at that time.

Treatment

After remission, we asked to all patients to enter in a follow-up study including clinical, endoscopic and histological evaluation under treatment with mesalazine or rifaximin.

Nineteen patients refused any further treatment, and were excluded from any further evaluation. One-hundred and eleven patients agreed to enter in one of treatment groups, as follows:

- 59 patients (group A) were treated with mesalazine 1.6 g/day;
- 52 patients (group B) were treated with rifaximin 800 mg/day for 7 days every month.

Endoscopy

After remission all patients agreeing to enter in the study were submitted to the same standard endoscopic control after 6, 12, and thereafter every 12 months. All patients underwent the same bowel preparation prescribed in our centers consisting of an oral polyethylene glycol solution to be taken in the evening. The day after a pancolonoscopy (clean colon colonoscopy) was performed and six biopsy samples of colonic mucosa were collected in the sigmoid tract for histological examination. Biopsies were taken from the mucosa between diverticula. Colonoscopy was again performed at the time of an eventual recurrence. Persistence of endoscopic inflammation was defined as detection of signs of inflammation (hyperemia, erosions, and petechiae) around the diverticular opening.

Written informed consent was obtained by all patients before entry in the study.

Histology

The presence of active inflammatory infiltrate was assessed by a semi-quantitative neutrophils count on 10 colonic fields with high power field (HPF) technique at 40x magnification, assessed both at the bottom and on the whole crypts, as already validated[10]. Hematoxylin and Eosin staining was performed to assess the histology of the sigmoid tract.

Neutrophilic infiltrate was also evaluated in order to assess active or non-active inflammation by using an arbitrary and semi-quantitative grading: non-active (absence of neutrophilic infiltrate, score = 0); mild active (focal presence of neutrophils, score=1); moderate (presence of neutrophils intermediate between mild and severe, score = 2); severe (diffuse neutrophilic infiltrate, score = 3). Neuthrophils were localized by myeloperoxidase staining as well as immunohistochemical reactivity using anti-CD15 monoclonal antibodies.

Also histological assessment was again performed at the time of recurrence. Persistence of active histological inflammation was defined as neutrophilic score at least = 1.

Clinical Assessment

An official control visit was performed after 6, 12, and thereafter every 12 months after obtaining remission. The presence of possible side-effects was evaluated. Patient compliance was assessed asking patients to return pills' box and counting the remaining pills at the control visit. In order to differentiate between persistent symptoms and recurrence of the disease, and since there isn't a widely accepted definition of recurrent diverticulitis in the medical literature, recurrence of diverticulitis was defined as return to our observation at least 30 days after the initial presentation of the disease because of abdominal pain with or without other symptoms (constipation or diarrhea and/or fever), associated with detection of increased fecal calprotectin. We used this test in case of patient's returning to our observation because it has been demonstrated effective in detecting colonic inflammation in DD and in distinguishing symptomatic DD from IBS, as well as in assessing response to therapy in DD[11]. In particular, we previously found that FC was increased in all patients suffering from AUD, as well as we found that FC decreased as response to therapy[11].

Moreover, the patients were invited to a control visit whenever they considered it necessary.

Statistical Analysis

The collection and analysis of data were performed by using MedacalcÆ 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 «2 test was used for categorical data. $p < 0.050$ was considered significant.

Results

The patients were followed for a maximum of 24 months. Seven patients were excluded from final evaluation because they were lost to follow-up. One hundred and four patients were available for the final assessment:

- 55 in group A (39 males, 16 females, mean age 58.5 ± 11 years);
- 49 in group B (24 males, 25 females, mean age 57 ± 11.6 years).

Mesalazine was the only therapeutic approach that guaranteed a significant higher percentage in maintaining remission at clinical follow-up (Figure 1).

Mesalazine was the only therapeutic approach able to maintain a statistically significant mucosal healing at endoscopic follow-up (Figure 2).

Mesalazine was the only therapeutic approach able to reduce the histological activity significantly (Figure 3).

Discussion

Diverticulitis represents a significant economic and clinical burden to the western Health Care Systems and its patients[12]. 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[12]. Similar results were described by a larger study[13]. Moreover, recent reports reported that recurrence rate of diverticulitis is 19-54% at 5 year follow-up[14,15]. 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[17], in preventing recurrence of diverticular disease and diverticulitis[17]. However, a recent position paper criticizes this approach, because of the high costs for National Health System and the lack of definitive results in preventing diverticulitis[18].

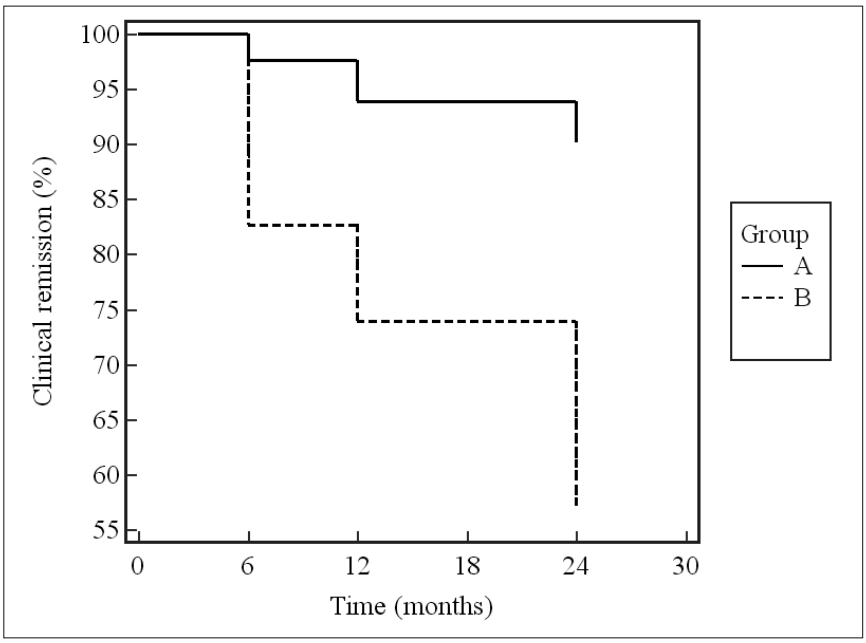

Figure 1. Clinical remission during follow-up in patients taking mesalazine (Group A) and rifaximin (Group B). $p = 0.002$.

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[4]. However, there are no studies comparing mesalazine and antibiotics in preventing recurrence of the diverticulitis.

We found that mesalazine is the only therapeutic approach able to maintain significantly remission after an attack of AUD. In this way, mesalazine seems to confirm what already obtained in preventing recurrence of symptomatic uncomplicated diverticular disease[19]. Rifaximin was ineffective in preventing diverticulitis relapse, and these results are clearly related to the persistence of the endoscopic/histological inflammation in patients taking rifaximin. This is probably related to the different mechanisms of these drugs. After resolution of acute inflamma-

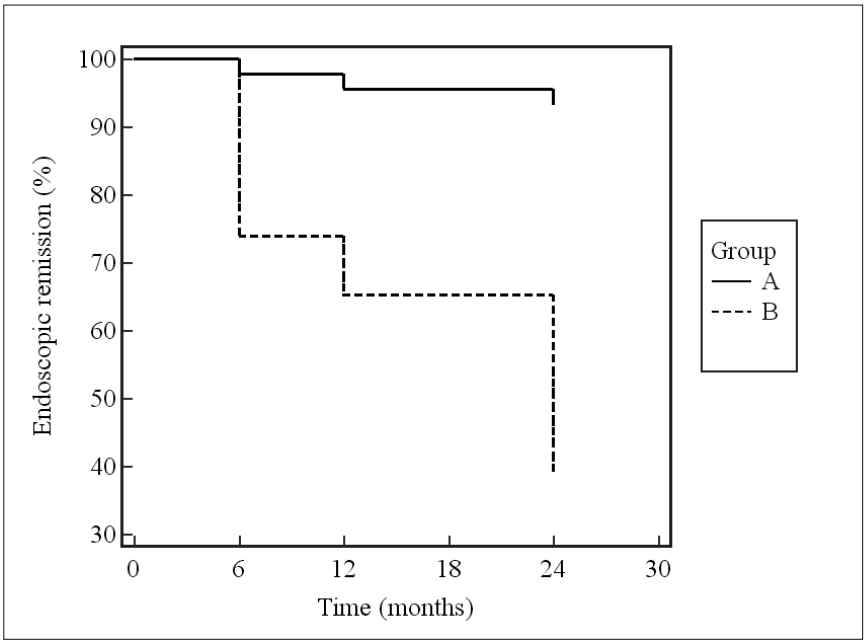

Figure 2. Endoscopic remission during follow-up in patients taking mesalazine (Group A) and rifaximin (Group B). $p = 0.000$.

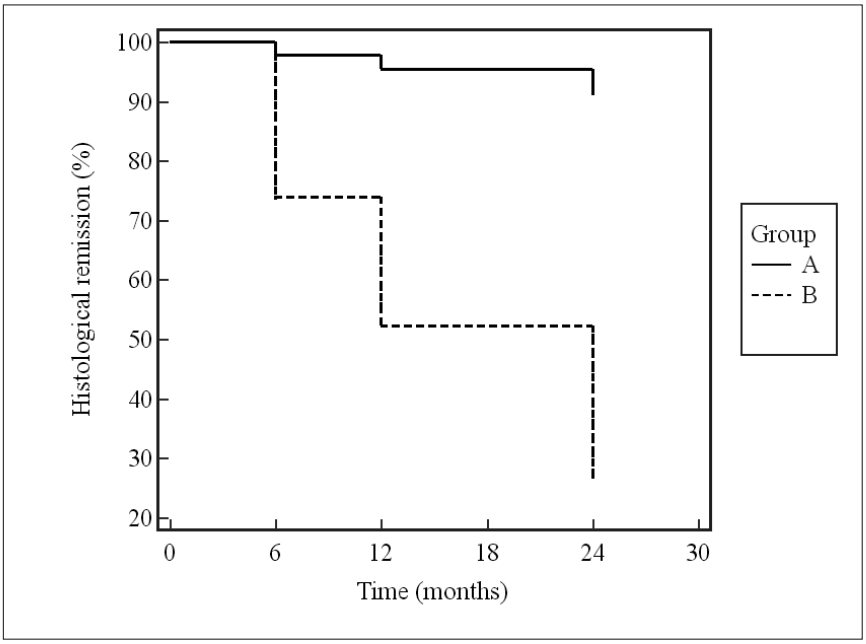

Figure 3. Histological remission during follow-up in patients taking mesalazine (Group A) and rifaximin (Group B). $p = 0.000$

tion, mesalazine can control histological inflammation and, therefore, prevent clinical recurrence of the disease[20], similar to what occurs in inflammatory bowel disease[21]. On the contrary, long-lasting rifaximin course does not seem to be effective in controlling this type of lesion. From a patho-physiological perspective, repeated oral administration of an antibiotic, which reaches very high concentrations within the gastrointestinal lumen, may have profound influence on the intestinal flora[22]. As expected, fecal bacterial counts fall down during oral treatment with rifaximin, but the effect is short lasting. In fact, the bacterial population (mostly *Escherichia coli*, *Bacterioides spp*. and anaerobic *cocci*) has been shown to recover within 1-2 weeks after the end of treatment[22]. This may, therefore, explain why long-lasting rifaximin strategyî was significantly worse than "long-lasting mesalazine strategy" in preventing recurrence of the diverticulitis. Some attempt may be performed in order to improve the efficacy of rifaximin in preventing diverticulitis relapses. One possibility may be to give rifaximin two times per month. For example, two 10 day courses with a 10 day interval between the two antibiotic courses may cover the entire month preventing the bacterial population recovery. Another possibility may be to increase rifaximin dosage up to 1200 mg/day, as recently advised in treating irritable bowel syndrome[23], or to give rifaximin for longer time, as recently advised in treating Crohn's disease[24,25]. However, we do not know whether and how this profound modification of colonic microflora may alter the immune system, and all the cited hypotheses should be confirmed by well-designed randomized investigations. At present, we know that endoscopic/histological inflammation seems to be an important factor in causing diverticulitis recurrence[26]. Mesalazine has been already shown effective in reducing histological inflammation in diverticular disease[27], while rifaximin failed to reach this result[28].

We know that some decision assumed in designing this study may be criticized. In particular, somebody may wonder why we performed early colonoscopy in patients with CT findings compatible with diverticulitis. Performing colonoscopy in acute diverticulitis is still controversial, because acute inflammation of the diverticula may be at risk of perforation or bleeding[29,30]. But recent literature data found that early colonoscopy (within 3 and 11 days after the admission) is as safe and effective as late colonoscopy (within 6 and 19 weeks following admission), without any complication in both approaches. We performed colonoscopy within 7 days after exclusion of complicated diverticulitis (which is considered the only parameter avoiding early colonoscopy[31]), and after a course of antibiotic therapy, and we did not record any complication. Somebody may argue that computerized tomography colonography (CTC) may have a better diagnostic potential for imaging of diverticu-

lar disease-specific findings, when compared with colonoscopy. Moreover, CTC is less uncomfortable and may be preferred by a majority of patients[32]. However, we hypothesized that persistence of endoscopic and histological inflammation under treatment may be the possible explanation for disease recurrence. On these bases, colonoscopy was performed in that patients to confirm this hypothesis. Of course, the safety of colonoscopy is an important issue in that patients. An adequate course of antibiotic therapy before colonoscopy is a good option to reduce the risk of perforation. We performed early colonoscopy after a 7 day course of antibiotic therapy, after careful clinical evaluation and after exclusion of free perforation by abdominal CT. None perforation was recorded during or after colonoscopy. So, our opinion is that gentle colonoscopy with minimal air insufflation can be carried out safely in that patients[33].

A limit of this reports is that is was an open fashion and not a randomized trial. However, it is un-doubtful that the results of this study are very interesting for clinical practice. We found for the first time that long-term treatment with mesalazine seems to be the best therapeutic strategy in preventing recurrence of diverticulitis, because it was the only treatment effective in reducing persistence of endoscopic/histological inflammation after an attack of AUD. On the contrary, rifaximin failed to reach these results.

These findings are surprising similar to what occur in inflammatory bowel disease, and lead to consider diverticulitis as a chronic disease requiring long-term treatment in order to prevent recurrence and complications.

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