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Long-term prevention of post-operative recurrence in Crohn's disease cannot be affected by mesalazine

C. Papi [a,*], A. Aratari [a], V. Tornatore [a], M. Koch [a], L. Capurso [a], R. Caprilli [b]

[a] *Gastroenterology Unit, S Filippo Neri Hospital, Rome, Italy*
[b] *Gastroenterology Unit, Department of Clinical Sciences, University of Rome "La Sapienza", Rome, Italy*

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Abstract

Background: Prevention of post-operative recurrence has a central role in the management of Crohn's Disease (CD). Many drugs have been evaluated in prospective randomised controlled trials (RCTs) but the results are disappointing. Mesalazine, the drug more extensively investigated, has been shown to be effective for preventing recurrence in the short-term; however, the overall benefit is small and no data are available on the long-term effectiveness.
Aim: To compare the long-term occurrence of post-operative recurrence in patients who received regular prophylactic treatment with mesalazine with patients who did not receive prophylaxis after the first radical resection for ileo-caecal CD.
Patients and methods: The records of 216 patients with ileo-caecal CD at their first resection were reviewed: 146 patients (67.6%) received post-operative prophylaxis with mesalazine while 70 patients (32.4%) received no prophylaxis. Allocation of patients in the two groups was determined by patients' preferences and by different policies in the post-operative prophylactic approach. The mean follow-up after surgery was 153.7 months (range 12–544). The co-primary endpoints were post-operative clinical and surgical recurrence. Statistical analysis: Kaplan–Meier survival method, Chi-square, Student *t*-test.
Results: The two groups were comparable with regard to gender, age at surgery, smoking habits, pattern of CD (perforating/not perforating), and disease duration before surgery. One year after surgery, a small, not statistically significant, risk reduction in clinical recurrence was observed in mesalazine treated group (−7.6%; 95% CI −18.0% to 2.8%). Within 10 years after surgery, the cumulative probability of clinical recurrence and surgical recurrence were similar in the two groups (Log Rank test $p=0.9$ and $p=0.1$ respectively).
Conclusion: Mesalazine prophylaxis is not effective for preventing the long-term post-operative recurrence in ileo-caecal Crohn's disease.

* Corresponding author. UOC Gastroenterologia, Ospedale S. Filippo Neri, Via Martinotti 20, 00135 Roma, Italy. Tel.: +39 06 33062245; fax: +39 06 33062245.
E-mail addresses: c.papi@sanfilipponeri.roma.it, c.papi@fastwebnet.it (C. Papi).

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1. Introduction

Most patients with Crohn's disease (CD) will require surgery during the course of their disease. However, surgery is not curative and post-operative recurrence is quite inexorable. It has been reported that one year after resection, 60–80% of patients have new lesions at the neo-terminal ileum (endoscopic recurrence), 10–20% will develop symptoms (clinical recurrence) and 5% will need further intestinal resection (surgical recurrence).[1,2] After 10 years, approximately 50% of patients will experience clinical recurrence and 35% will need re-operation.[3]

Prevention of post-operative recurrence is therefore considered to be a central problem in the management of CD.[4] Several drugs have been evaluated as prophylactic treatment in randomised controlled trials (RCTs) and meta-analysis: these include mesalazine,[5–12] antibiotics (metronidazole and ornidazole),[13,14] budesonide,[15–17] azathioprine or mercaptopurine,[18,19] interleukin-10,[20] and, more recently, probiotics.[21–23]

Mesalazine is the drug more extensively evaluated. Several RCTs have been published from 1994 to 2000.[5–9] A meta-analysis published in 1997,[10] and subsequently updated in 2000[11] and 2002,[12] showed a little but significant effect of mesalazine for reducing clinical recurrence. The overall risk difference (RD) is −10% (95% CI −16.9% to −3.2%; $p=0.0041$), and the number of patients needed to treat (NNT) to prevent one recurrence is 10. A more relevant effect has been reported for preventing endoscopic recurrence and, in particular, severe endoscopic recurrence, with an overall reduction of risk of 18% and of 20%, respectively.[2,12] A meta-regression of all the studies published has shown that prolonged disease duration and ileal location are predictors of better response.[10] It is not clear which is the optimal dose of mesalazine, but a study comparing 2.4 g vs. 4 g daily did not show a significant difference between the two doses.[24] In a recent systematic review, addressing the potential influence of different mesalazine formulations on maintenance of remission in CD, it has been shown that pH 7-dependent mesalazine seems to be more effective than pH 6-dependent and controlled release formulations.[25]

Based on the available evidence (evidence grade A), major guidelines from the British Society of Gastroenterology,[26] the European Crohn's and Colitis Organisation,[27] and the American College of Gastroenterology[28] recommend post-operative prophylactic treatment with mesalazine for at least 18–24 months after surgical resection. Nevertheless, some authors continue to not recommend regular post-operative prophylaxis for all patients.[29,30] The efficacy of prophylactic treatment with mesalazine has been extensively investigated in the short-term after surgery (1–3 years) while no data are available on the long-term.

The aim of the present study was, therefore, to evaluate the long-term occurrence of post-operative recurrence comparing patients who received regular mesalazine treatment with patients who did not receive any prophylactic treatment after the first radical resection for ileo-caecal CD.

2. Patients and methods

The records of 679 patients with established diagnosis of CD referred to our two GI Units in Rome (Gastroenterology Unit, San Filippo Neri Hospital, Rome, Italy and Department of Clinical Sciences, University of Rome "La Sapienza", Rome, Italy) were retrospectively reviewed. Patients who had undergone at least one radical surgical resection for ileal disease (with or without right colon involvement), and with at least one year of post-operative follow-up, were included in the study. According to mesalazine prophylactic treatment of post-operative recurrence patients were divided into two groups:

- Group 1: patients who had received continuative post-operative prophylactic treatment with mesalazine;
- Group 2: patients who had not received any post-operative prophylactic treatment.

Allocation of patients in the two groups was determined by patients' preferences and by different policies in the post-operative prophylactic approach. In our current clinical practice, after ileo-caecal resection for CD, we encourage all patients to stop smoking and start mesalazine 2.4 g/day within 2 weeks after operation. Prophylactic treatment is maintained for at least 2 years, but generally it is continued indefinitely or until severe endoscopic recurrence or clinical recurrence occurs. This strategy is discussed with each patient and information concerning the little benefit of mesalazine is given. As a consequence, some patients prefer to be off of tablets in the post-operative setting, after a long pre-operative history of medical treatment. In addition, some patients were referred to our institutions months or years after operation performed in other hospitals where post-operative prophylactic treatment was not applied. Few patients that were started on mesalazine and did not tolerate the medication were allocated in group 2. Clinical and demographic characteristics of all patients were recorded: gender, age at the time of surgery, smoking habits, pattern of CD according to the surgical specimen (penetrating/not penetrating), disease duration (from diagnosis to surgery) and timing of surgery (before or after 3 years from diagnosis).

Table 1 Flow chart of the study.

Patients reviewed	679
Ileo-caecal CD with at least 1 "radical" resection (eligible population)	222/679 (33%)
Complete follow up data: at least 1 year of follow up (included in the analysis)	216/222 (97%)
Post-operative 5-ASA prophylaxis (group 1)	146 (67.6%)
No post-operative 5-ASA prophylaxis (group 2)	70 (32.4%)
Mean post-operative follow up months (range)	153.7 (12–544)