

## Reducing the incidence of post-operative recurrence in Crohn's disease patients

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The long-term management of Crohn's disease remains a challenge. The gastroenterologist is often faced with intractable or complicated forms of the disease that make surgical intervention unavoidable despite the numerous options of conservative treatment available. Almost 80% of Crohn's patients will require surgical resection eventually. The recurrence rate after surgical resection is very high. Within one year after operation as many as 95% of patients will exhibit endoscopic recurrence of the disease, while by the third post-operative year clinical recurrence is as high as 65%. The necessity of reoperation increases with time after the first resection. As many as 38% of the patients will require a second resection within 5 years, 57% within a decade and as many as 71%, twenty years down the line.

Numerous medical treatments have been tried in an attempt to significantly decrease the post-surgical recurrence of Crohn's. Sulfasalazine and mesalazine, metronidazole and ornidazole, prednisolone and budesonide and finally azathioprine and 6-mercaptopurine are the main drugs tried in numerous trials over the last 25 years.

Historically, sulfasalazine was first tried in an attempt to maintain remission after surgical resection. However, placebo-controlled trials failed to show any significant benefit.<sup>1,2,3</sup>

Oral corticosteroids and budesonide, although invaluable in the management of the acute phase of the disease, did not seem to have any significant effect on the prevention of recurrence.<sup>1,4-7</sup>

Another type of medication that has been extensively used in the management of inflammatory bowel disease, and was eventually tried in the prevention of post-surgical recurrence of Crohn's disease, is mesalazine (mesalamine or 5-ASA).

Six randomized trials were conducted between 1994 and 2000, looking into the effect of mesalazine in the post-operative recurrence of Crohn's disease.

Two of them, one using Eudragit-coated, pH-dependent release formulation of mesalamine (Salofalk and Rowasa, 3gr/day),<sup>8</sup> and one using a methylcellulose-covered microgranule preparation of mesalazine (Pentasa, 3gr/day)<sup>9</sup>, showed some significant benefit compared to placebo. The first study claimed a 19% reduction of clinical recurrence compared to placebo, in a follow-up period up to 6 years, while the second study focused on the prevention of endoscopic recurrence, showing a 36% reduction compared to placebo (50% vs 14%). In the latter, however, no significant improvement in clinical recurrence was observed, while, at the same time, the small number of the patients included, compromised the safety of the conclusions.

With regard to the rest of the trials, pH-dependent release formulations of mesalazine (Pentasa, Asacol and Claversal), at similar doses (3-4gr/day), were used and they all failed to indicate any statistically significant impact on the post-operative recurrence of Crohn's.<sup>10-13</sup>

Interestingly a meta-analysis of four of those studies<sup>14</sup> found a 13.1% reduction in disease recurrence rate with mesalazine ( $p=0.0028$ , CI 95% from -21.8% to -4.5%). That would be a reason for optimism if it were not for the results of the most rigorously conducted study with the largest number of patients included,<sup>10</sup> and thus probably the most reliable, that failed to show any statistically significant benefit of mesalazine vs placebo.

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In conclusion, mesalazine probably does not reduce the post-operative recurrence of Crohn's disease.

Imidazole antibiotics (metronidazole and ornidazole) have been tried both for their antimicrobial and immunomodulatory properties.

Placebo controlled studies<sup>15</sup> were conducted using metronidazole 20mg/kg/day and ornidazole 1,000mg/day. Metronidazole, when used for 12 weeks, was shown to be effective in the prevention of endoscopic recurrence in the first three post-operative months but clinical remission was not sustained for the first year after resection. Ornidazole on the other hand, prevented endoscopic recurrence within the first 12 weeks post-operatively and maintained clinical remission for a year, when used for 52 consecutive weeks, but the beneficial effect did not extend to the second and third post-op years. In addition to the short-lived beneficial effect of imidazole antibiotics, the development of significant side-effects (peripheral neuropathy, taste disturbance, dizziness and various gastrointestinal symptoms, in particular when Ornidazole was administered for up to 52 weeks) in long-term use, rendered them impractical for the maintenance of remission of the disease post-operatively.

Another category of medication that has been used with promising results in the prevention of recurrence of Crohn's disease are the purine antimetabolites, azathioprine and 6-mercaptopurine(6-MP).

Initially, a small, uncontrolled study<sup>16</sup> showed efficacy of 6-MP for the prevention of post-operative recurrence of Crohn's.

Subsequently two more studies were published exploring the preventive potential of purine antimetabolites as compared to mesalazine.

The first was a randomized, blind, placebo controlled study<sup>17</sup> that included 131 patients, treated with either a fixed dose of 6-MP (50mg/day) or with 3gr/day of mesalazine (Pentasa) for 2 years. The patients were followed-up with evaluation of clinical parameters (notably without the implementation of any validated quantitative scoring system) every three months and with colonoscopy at months 6, 12 and 24 after surgery. Clinical recurrence rates for the 6-MP, the mesalazine and the placebo group were 50%, 58% and 77% respectively at the end of the second year (CI 95%). Based on these data, the authors claimed a benefit of 6-MP vs placebo (HR, 0.52;p=0.045) and a trend for mesalazine vs placebo (HR, 0.62;p=0.123). As far as endoscopic recurrence is concerned, the relapse rates for 6-MP, mesalazine and placebo were 43%, 63% and

64% respectively (CI 95%), that showing a benefit in the 6-MP group. Additionally, for high scores of recurrence severity, (Rutgeerts' endoscopic recurrence severity grade >2) the benefit seems even higher with respective endoscopic recurrence rates for the three groups of 16%, 48% and 42%. The extraordinarily higher clinical recurrence rate as compared to the endoscopic recurrence is presumably the result of the lack of implementation of a validated quantitative clinical recurrence scoring system, such as the CDAI. It is also of note that the dose of 6-MP used in the study was very low compared to the dose used for other conditions (usually 1-1.5 mg/kg/day), a compromise undertaken by the investigators to minimise the withdrawal rate due to side effects (leukopenia, thrombocytopenia, liver biochemistry abnormalities, pancreatitis, renal impairment). Overall the study suggests a benefit from 6-MP compared to placebo and a numerical but not statistically significant benefit of 6-MP compared to mesalazine, and underlines the need for of further studies with graded doses of 6-MP.

The second randomised, open label study<sup>18</sup> enrolled 142 patients who were treated with either azathioprine (2mg/kg/day) or mesalazine (Pentasa) (3gr/day), for 2 years. The included patients were followed-up on a 6 monthly basis with assessment of CDAI score and other clinical and haematological/biochemical parameters such as full blood count and C-reactive protein levels. The clinical relapse rates given in the results of the study for the 6-MP and the mesalazine groups were 17% and 28% (CI 95%) respectively. No statistically significant difference between the two groups was documented.

In conclusion, from the existing data, the most promising option in our attempt to prevent recurrence of Crohn's after surgery, appears to be the group of purine antimetabolites (azathioprine, 6-MP). However, the low power data produced by existing studies, in combination with the potential side-effects of the purine antimetabolites, outline the need for further studies, with adequate numbers of patients enrolled, to allow the extraction of statistically significant conclusions and justify their use as standard medications for the prevention of Crohn's relapse after surgery.

## REFERENCES

1. Bergman L, Krause U. Postoperative treatment with corticosteroids and salazosulphapyridine (Salazopyrin) after radical resection for Crohn's disease. *Scand J Gastroenterol* 1976; 11:651-656.
2. Wenckert A, Kristensen M, Eklund AE, Barany F, Jarnum S, Worning H, Folkenborg O, Holtz A, Bonnevie O,

- Riis P. The long-term prophylactic effect of salazosulphapyridine (Salazopyrin) in primarily resected patients with Crohn's disease. A controlled double-blind trial. *Scand J Gastroenterol* 1978; 13:161-167.
3. Ewe K, Herfarth C, Malchow H, Jesdinsky HJ. Postoperative recurrence of Crohn's disease in relation to radicality of operation and sulfasalazine prophylaxis: a multicenter trial. *Digestion* 1989; 42:224-232.
  4. Smith RC, Rhodes J, Heatley RV, Hughes LE, Crosby DL, Rees BI, Jones H, Evans KT, Lawrie BW. Low dose steroids and clinical relapse in Crohn's disease: a controlled trial. *Gut* 1978; 19:606-610.
  5. Malchow H, Ewe K, Brandes JW, Goebell H, Ehms H, Sommer H, Jesdinsky H. European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. *Gastroenterology* 1984; 86:249-266.
  6. Hellers G, Cortot A, Jewell D, Leijonmarck CE, Lofberg R, Malchow H, Nilsson LG, Pallone F, Pena S, Persson T, Prantera C, Rutgeerts P. Oral budesonide for prevention of postsurgical recurrence in Crohn's disease. The IOIBD Budesonide Study Group. *Gastroenterology* 1999; 116:294-300.
  7. Ewe K, Bottger T, Buhr HJ, Ecker KW, Otto HF. Low-dose budesonide treatment for prevention of postoperative recurrence of Crohn's disease: a multicentre randomized placebo-controlled trial. *German Budesonide Study Group. Eur J Gastroenterol Hepatol* 1999; 11:277-282.
  8. McLeod RS, Wolff BG, Steinhart AH, Carryer PW, O'Rourke K, Andrews DF, Blair JE, Cangemi JR, Cohen Z, Cullen JB. Prophylactic mesalamine treatment decreases postoperative recurrence of Crohn's disease. *Gastroenterology* 1995; 109:404-413.
  9. Brignola C, Cottone M, Pera A, Ardizzone S, Scribano ML, De Franchis R, D'Arienzo A, D'Albasio G, Pennestri D. Mesalamine in the prevention of endoscopic recurrence after intestinal resection for Crohn's disease. Italian Cooperative Study Group. *Gastroenterology* 1995; 108:345-349.
  10. Lochs H, Mayer M, Fleig WE, Mortensen PB, Bauer P, Genser D, Petritsch W, Raithel M, Hoffmann R, Gross V, Plauth M, Staun M, Nesje LB. Prophylaxis of postoperative relapse in Crohn's disease with mesalamine: European Cooperative Crohn's Disease Study VI. *Gastroenterology* 2000; 118:264-273.
  11. Sutherland LR, Martin F, Bailey RJ, Fedorak RN, Poleski M, Dallaire C, Rossman R, Saibil F, Lariviere L. A randomized, placebo-controlled, double-blind trial of mesalamine in the maintenance of remission of Crohn's disease. The Canadian Mesalamine for Remission of Crohn's Disease Study Group. *Gastroenterology* 1997; 112:1069-1077.
  12. Caprilli R, Andreoli A, Capurso L, Corrao G, D'Albasio G, Gioieni A, Assuero LG, Paladini I, Pallone F, Ponti V. Oral mesalazine (5-aminosalicylic acid; Asacol) for the prevention of post-operative recurrence of Crohn's disease. Gruppo Italiano per lo Studio del Colon e del Retto (GISC). *Aliment Pharmacol Ther* 1994; 8:35-43.
  13. Florent C, Cortot A, Quandale P, Sahmound T, Modigliani R, Sarfaty E, Valleur P, Dupas JL, Daurat M, Faucheron JL, Lerebours E, Michot F, Belaiche J, Jacquet N, Soule JC, Rothman N, Gendre JP, Malafosse M. Placebo-controlled clinical trial of mesalazine in the prevention of early endoscopic recurrences after resection for Crohn's disease. Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID). *Eur J Gastroenterol Hepatol* 1996; 8:229-233.
  14. Camma C, Giunta M, Rosselli M, Cottone M. Mesalamine in the maintenance treatment of Crohn's disease: a meta-analysis adjusted for confounding variables. *Gastroenterology* 1997; 113:1465-1473.
  15. Rutgeerts P, Hiele M, Geboes K, Peeters M, Penninckx F, Aerts R, Kerremans R. Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection. *Gastroenterology* 1995; 108:1617-1621.
  16. Korelitz BI, Adler DJ, Mendelsohn RA, Sacknoff AL. Long-term experience with 6-mercaptopurine in the treatment of Crohn's disease. *Am J Gastroenterol* 1993; 88:1198-1205.
  17. Hanauer SB, Korelitz BI, Rutgeerts P, Peppercorn MA, Thisted RA, Cohen RD, Present DH. Postoperative maintenance of Crohn's disease remission with 6-mercaptopurine, mesalamine, or placebo: a 2-year trial. *Gastroenterology* 2004; 127:723-729.
  18. Ardizzone S, Maconi G, Sampietro GM, Russo A, Radice E, Colombo E, Imbesi V, Molteni M, Danelli PG, Taschieri AM, Bianchi PG. Azathioprine and mesalamine for prevention of relapse after conservative surgery for Crohn's disease. *Gastroenterology* 2004; 127:730-740.