

## Review article: can post-operative recurrence in Crohn's disease be prevented?

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### SUMMARY

The decision regarding prophylactic treatment after surgery in Crohn's disease (CD) requires a good estimation of the risk of recurrence. It is also important to consider the consequences of recurrence for the patient, and the risks and benefits of treatment, bearing in mind that it will be given over a long period.

Several drugs have been tried to decrease the risk of recurrence. Corticosteroids and budesonide have proved to be ineffective. Mesalazine has significant efficacy in some, but not all trials, and a meta-analysis has established that it decreases the absolute risk by 10–15% after 1–2 years. Mercaptopurine seemed to be effective in a recent study. Metronidazole and ornidazole have significant efficacy, but cannot be tolerated for long periods. Probiotics represent a new approach, but evidence for their efficacy in CD is still lacking.

In the past, the strategy was to give no treatment until clinical recurrence. Another approach is to give no treatment, and then to treat the patient according to severity of endoscopic recurrence. Alternative strategies include treating all patients with mesalazine until either severe endoscopic or clinical recurrence occurs, and then to use azathioprine/mercaptopurine, or to give azathioprine/mercaptopurine immediately, especially in high-risk patients.

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## INTRODUCTION

Preventing post-operative recurrence in Crohn's disease (CD) is a complex problem. The decision regarding treatment after surgery first requires a good estimation of the risk of recurrence. It is also important to consider the consequences of recurrence for the patient, and the risks and benefits of treatment, bearing in mind that it will be given over a long period. More than 70% of CD patients are operated on during their lifetime. New lesions recur early after ileocolonic resection and this often leads to clinical recurrence and eventual reoperation. Median time to surgical recurrence is 10–20 years, to clinical recurrence 3–5 years and to endoscopic recurrence 6 months.<sup>1</sup> Among factors predicting recurrence, smoking clearly increases the risk,<sup>2–5</sup> as does the presence of an anastomosis.<sup>1</sup> Penetrating behaviour is also associated with a higher risk of recurrence in most studies.<sup>6</sup> Lesions usually reappear at the site of the anastomosis and/or proximally.

## MEDICATIONS FOR PREVENTION OF RECURRENCE

Several drugs have been evaluated to decrease the risk of recurrence in CD, including mesalazine, metronidazole or ornidazole, budesonide, azathioprine or mercaptopurine, interleukin-10, and more recently, probiotics. Demonstration of a reduction in the risk of clinical recurrence requires inclusion of a large number of patients, because the spontaneous risk within the 2 years following surgery is relatively low (20–40%). Severity of endoscopic recurrence has been shown to predict the delay of clinical recurrence.<sup>7, 8</sup> For this reason, endoscopic recurrence has been used as a primary endpoint in several studies (Table 1). Another advantage of using endoscopic recurrence as the primary efficacy variable is that the Clinical Disease Activity Index (CDAI) is probably less accurate in the post-operative setting than in other clinical situations.<sup>9</sup> Reproducibility of the Rutgeerts post-operative endoscopic score has, however, not been prospectively validated, and the definition of endoscopic recurrence based solely on the use of a cut-off value remains questionable.

Table 1. Randomized controlled trials of mesalazine for prevention of post-operative recurrence in Crohn's disease

Reference	No. of patients	Daily dose (g)	Duration (months)	Recurrence rate (%)			P	Clinical (CR) or endoscopic (ER)* recurrence
				5-ASA	Placebo	Other		
Mc Leod <sup>9</sup>	163	3	36 (up to 72)	31	41	–	0.03	CR
Brignola <sup>10</sup>	87	3	12	24	56	–	0.004	Severe ER
				16	23	–	N.S.	CR
Florent <sup>11</sup>	126	3	3	50	63	–	N.S.	ER
Caprilli <sup>†12</sup>	110	2.4	24	52	85 <sup>†</sup>	–	0.002	ER
				18	41 <sup>†</sup>	–	0.006	CR
Sutherland <sup>13</sup>	66	3	12	10	23	–	N.S.	CR
Lochs <sup>14</sup>	318	4	18	24	31	–	N.S.	CR
	124 <sup>‡</sup>			22 <sup>‡</sup>	40 <sup>‡</sup>	–	0.02 <sup>‡</sup>	CR <sup>‡</sup>
Campieri <sup>15</sup>	40	4	12	40	–	20 <sup>§</sup>	<0.05	ER
Caprilli <sup>21</sup>	206	2.4 vs. 4	12	43 vs. 33	–	–	N.S.	ER
				14 vs. 12	–	–	N.S.	CR
Hanauer <sup>¶16</sup>	131	3	24	86	98	68 <sup>¶</sup>	0.12	ER
				61	70	53 <sup>¶</sup>	N.S.	CR
Ardizzone <sup>¶17</sup>	142	3	24	30	–	20 <sup>¶</sup>	N.S.	Clinical relapse**

\*Endoscopic recurrence: Rutgeerts score >1; severe ER: Rutgeerts score >2.

<sup>†</sup>Not blinded; comparison with no treatment.

<sup>‡</sup>Small bowel resection only.

<sup>§</sup>Vs. rifaximin then VSL#3.

<sup>¶</sup>Vs. mercaptopurine or azathioprine.

\*\*Noncurative surgery.

## Mesalazine

Some, but not all, randomized controlled trials<sup>10–17</sup> have demonstrated that mesalazine administered immediately after surgery was able to reduce clinical or endoscopic post-operative recurrence (Table 1). Three meta-analyses were published by the same authors.<sup>18–21</sup> The first, by Cammà *et al.*<sup>19</sup> in 1997, included four trials ( $n = 411$ ). The reduction in the absolute risk of clinical recurrence with mesalazine compared with placebo was 13.1% [95% confidence interval (CI):  $-21.8\%$  to  $-4.5\%$ ;  $P = 0.003$ ]. The second meta-analysis by Cottone and Cammà<sup>20</sup> took into account a more recent and large trial, the European Cooperative Study<sup>15</sup> including 318 patients, which failed to demonstrate a significant preventive effect of mesalazine 4 g/day. A subgroup of 124 patients who had a curative resection for isolated small bowel involvement did, however, benefit from the study drug. In the meta-analysis, the reduction in the absolute risk of clinical recurrence was only 10% (95% CI:  $16.9$  to  $-3.2\%$ ;  $P = 0.004$ ). The number of patients treated to prevent one recurrence (NNT) in the first 2 years was 10. The results remained significant after exclusion of the open-label trial from Caprilli *et al.*<sup>13</sup> The meta-analysis has been updated after the results of the GISC Study<sup>22</sup> comparing mesalazine 2.4 g/day with 4.8 g/day (not significant), but results of this meta-analysis including 1141 patients have not yet been fully published. In an abstract<sup>21</sup> and a recent review,<sup>3</sup> the authors report a reduction in clinical recurrence of 15% (NNT = 6.6) and of endoscopic recurrence of 18% (NNT = 5.5). In addition, a more recent trial, comparing mesalazine, mercaptopurine and placebo (see below) was not included in the meta-analysis.<sup>17</sup> These data suggest a small but significant benefit of mesalazine (2.4–4 g/day) to prevent clinical recurrence after a surgical operation.

## Antibiotics

Metronidazole (20 mg/kg/day) was compared with a placebo in 60 patients who had undergone a right ileocolic resection.<sup>23</sup> Treatment began within the 7 days following surgery and was continued for 3 months. At month 3, an endoscopic recurrence was found in 75% of patients in the placebo group vs. 52% of patients in the metronidazole group (not significant). Severe endoscopic recurrences were, however, less frequent in the metronidazole group (13% vs. 43%;  $P = 0.02$ ). After

3 years of follow-up, endoscopic recurrence rates were identical (82% vs. 78%). Another trial<sup>8</sup> from the same Belgian group demonstrated the effectiveness of ornidazole 1 g/day given orally during 1 year. Recurrence rates were significantly lower in the ornidazole group than in the placebo group (8% vs. 37%;  $P = 0.002$  for clinical recurrence and 54% vs. 79%;  $P = 0.04$  for endoscopic recurrence), but again, after 3 years of follow-up, clinical recurrence rates were similar. Discontinuation and side-effect rates were also significantly higher in the ornidazole group than in the placebo group (32% and 68% vs. 12% and 30%, respectively). These data show that imidazoles are effective for the prevention of recurrence, but the duration of their administration is limited by toxicity.

## Mercaptopurine and azathioprine

A study initially reported in 1998<sup>24</sup> was fully published in 2004.<sup>17</sup> Five US centres randomized 131 patients after curative surgery to receive mercaptopurine (50 mg daily), mesalazine (3 g daily) or placebo in a double-blind, double-dummy trial. Due to patient withdrawals, only 69% of the study population was evaluable for the clinical recurrence endpoint. Clinical recurrence rates (intent to treat) by life-table analysis at 24 months were 50%, 58% and 77% in patients receiving mercaptopurine, mesalazine and placebo, respectively. Endoscopic recurrence rates were 43%, 63% and 64%. Mercaptopurine was more effective than placebo ( $P < 0.05$ ) in preventing clinical and endoscopic recurrence over 2 years. There was a trend for a benefit for mesalazine compared with placebo for clinical recurrence ( $P = 0.12$ ) but not for endoscopic recurrence ( $P = 0.45$ ), but no significant difference was found between mesalazine and mercaptopurine. This study has several drawbacks: the dose of mercaptopurine used by the patients was relatively low, the rate of study withdrawal was high, as was the rate of clinical recurrence, which was even higher than the endoscopic recurrence rate.

In the same issue of *Gastroenterology*, a prospective, open-label, randomized study, including 142 patients who have undergone conservative surgery for CD was published by Ardizzone *et al.*<sup>18</sup> Patients received azathioprine (2 mg/kg daily) or mesalazine (3 g daily). After 24 months, the risk of clinical relapse was comparable in the azathioprine and mesalazine groups (odds ratio: 2.04; 95% CI: 0.89–4.67). No difference was observed with respect to surgical relapse. Azathioprine was more effective than mesalazine in

preventing clinical relapse in a subgroup of patients with previous intestinal resection.

In summary, the efficacy of azathioprine and mercaptopurine for the prevention of post-operative recurrence in patients with CD remains uncertain.<sup>25</sup>

### Corticosteroids

In a Cochrane review,<sup>26</sup> including three randomized placebo-controlled trials where classical corticosteroids were given for maintenance of remission induced by surgical or medical therapy, steroids did not appear to reduce the risk of relapse over a 24-month period of follow-up.

Two trials evaluated the effect of budesonide (3 and 6 mg/day, over 1 year) for prevention of postoperative recurrence.<sup>27, 28</sup> In the meta-analysis including 212 patients,<sup>29</sup> neither the endoscopic recurrence rate (odds ratio: 0.87; 95% CI: 0.5–1.49) nor the clinical recurrence rate (odds ratio: 0.88; 95% CI: 0.48–1.60) were significantly reduced.

### Probiotics

An open-label trial in 40 patients compared mesalazine 4 g daily with a treatment combining rifaximin 1.8 g daily for 3 months, followed by a probiotic mixture VSL#3 (6 g daily) for 9 months.<sup>16</sup> Results presented in 2000 were not fully published. The rates of endoscopic recurrence at 1 year were 40% and 20%, respectively. It is, however, unclear which of the two combined drugs the benefit could be attributed to.

A randomized placebo-controlled study was conducted in Italy to determine whether *Lactobacillus* GG, given for 1 year, could prevent Crohn's recurrent lesions after surgery or reduce their severity.<sup>30</sup> Of 15 patients in clinical remission on *Lactobacillus*, nine (60%) had endoscopic recurrence compared with 6 of 17 (35.3%) on placebo ( $P = 0.297$ ). There were no significant differences in the severity of the lesions between the two groups.

The probiotic strain *Lactobacillus johnsonii* LA1 was also tested in this setting. A randomized, double-blind, placebo-controlled study was conducted in France by the Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives in 97 patients who had undergone surgical resection <1 m.<sup>31</sup> The primary endpoint was endoscopic recurrence at 6 months, with grade >1 in Rutgeerts score. Endoscopic recurrence was observed in 30/47 patients (64%) in the placebo

group, and 21/43 (49%) in the LA1 group ( $P = 0.15$ ). Endoscopic score distribution did not differ significantly between the LA1 and placebo groups. At the same time, a multicentre, prospective, randomized, placebo-controlled clinical trial was conducted in Belgium with LA1 in 70 patients after ileocaecal resection.<sup>32</sup> After 12 weeks, the mean endoscopic score was not different between LA1 and placebo ( $1.41 \pm 1.31$  vs.  $1.05 \pm 1.21$ , respectively; not significant). The percentage of patients with mild (i1 + i2) or severe endoscopic recurrence (i3 + i4) was not significantly different between the two groups (mild: 45.2% vs. 39.3%, severe: 27.9% vs. 33%). There was no difference between the two groups for histological score, CDAI and serum C-reactive protein level.

This shows there is insufficient evidence for a beneficial effect of probiotics on post-operative recurrence in patients with CD. However, results obtained with one strain cannot be extrapolated to other strains or dosages, and negative results should not hinder the search for other ecological treatments, such as combination therapy with probiotics plus antibiotics, a mixture of probiotics or synbiotics.

### Other treatments

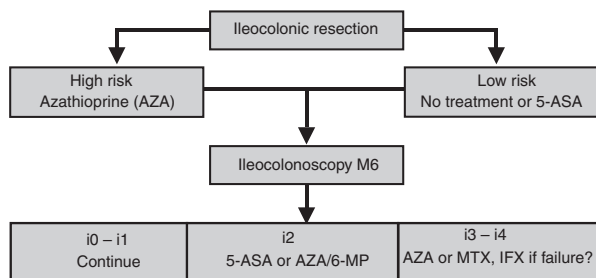
Interleukin-10 (4 or 8  $\mu\text{g}/\text{kg}$  subcutaneously, twice weekly) was compared with placebo in 60 patients after an ileocolic resection. At 3 months, endoscopic recurrence rates were 46% in the group treated with interleukin-10 and 52% in the group treated with placebo (not significant); 9% of patients had severe endoscopic lesions in both groups.<sup>33</sup>

A preparation of omega-3 fatty acids (Purepa) was used to prevent post-operative recurrence in a randomized double-blind placebo-controlled study including 50 patients after ileal resection.<sup>34</sup> Results presented in 1997 were never fully published. At 1 year, the rate of severe endoscopic recurrence (Rutgeerts score >2) was lower in the omega-3 group compared with the placebo group (ITT: 34% vs. 62%;  $P = 0.04$ ).

No data are available concerning methotrexate, infliximab and other biologics, tacrolimus, ciclosporin and mycophenolate mofetil for post-operative prophylaxis.

## STRATEGIES FOR POST-OPERATIVE PREVENTION

In the past, the strategy based on surgical series with low rates of recurrence was to withhold treatment



**Figure 1.** Example of post-operative strategy based on endoscopy (high risk: extensive or repeated surgery and/or perforating disease). MP, mercaptopurine; MTX, methotrexate; IFX, infliximab. Clinical recurrence based on Rutgeerts score: i0–i1, absence or rare lesions at the first endoscopic control; i2, moderate lesions; i3–i4, diffuse lesions and anastomotic ulcers or stricture.

until clinical recurrence ('wait and see'). Another approach is to give no treatment immediately after surgery, to perform an endoscopy 6–12 months later and to treat the patient according to the severity of endoscopic recurrence ('wait and scope'). One proposal is given in Figure 1. An alternative strategy is to treat all patients with 5-aminosalicylate until either severe endoscopic or clinical recurrence occurs, and then to use azathioprine/mercaptopurine. A more aggressive approach is to give azathioprine/mercaptopurine immediately.

topurine immediately. These strategies are discussed in Table 2.

In 2004, the ECCO consensus<sup>6</sup> concluded that all patients should be encouraged to quit smoking. Prophylactic treatment was also recommended after small intestinal resection and the drug of choice was mesalazine >2 g daily. Azathioprine/mercaptopurine should be considered as first-line therapy in high-risk patients. Prophylaxis was recommended within 2 weeks of surgery and should be continued for at least 2 years, although there is no reason to stop prophylactic treatment.

## CONCLUSION

The choice of pharmacological treatment for the prevention of post-operative recurrence in CD relies, to a great extent, on an informed estimation of the risk of recurrence. Mesalazine has small benefits in the post-operative setting in preventing clinical recurrence. Imidazoles have also proved effective, although toxic effects limit their use. More studies are needed to confirm the results of clinical studies that have demonstrated a low risk of recurrence in patients treated with mercaptopurine or azathioprine. Corticosteroids, probiotics and interleukin-10 have demonstrated no clinical benefit. The single most important lifestyle recommendation is to give up smoking.

**Table 2.** Strategies for the prevention of post-operative recurrence

Strategies	Advantages	Disadvantages
No treatment until clinical recurrence ('wait and see')	Lower cost	Risk of repetitive surgery
No treatment until severe endoscopic recurrence ('wait and scope')	Tailored treatment	Cost, risk and acceptance of colonoscopy
Mesalazine	Lower toxicity	Higher cost Lower efficacy Duration of treatment unknown
Azathioprine/mercaptopurine	Higher efficacy (uncertain)	Cost (drug + monitoring) Higher toxicity Duration of treatment unknown
Mesalazine and endoscopy, azathioprine if severe recurrence	Tailored treatment	Cost Cost, risk and acceptance of colonoscopy
Imidazole and endoscopy, mesalazine or azathioprine according to severity	Tailored treatment	Cost Toxicity of antibiotics Cost, risk and acceptance of colonoscopy

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