Debate

PROTAGONIST

Crohn's disease recurrence can be prevented after ileal resection

P Rutgeerts

The majority of patients suffering from Crohn's disease will undergo at least one surgical resection of the bowel in the course of their disease. Surgery greatly improves the quality of life in these patients but the beneficial effect is only temporary.

After ileal or ileocolonic resection there is a 20–30% symptomatic recurrence rate in the first year after surgery, with a 10% increase in each subsequent year. Most patients will eventually suffer recurrence, and a reoperation rate of 50–60% is generally reported. The need for simple and effective prophylactic therapy after bowel resection for Crohn's disease is great.

The natural evolution of postoperative Crohn's recurrence has been well studied. After curative resection of the inflamed bowel (that is, removal of all macroscopically involved gut) the disease recurs within weeks to months proximal to the ileocolonic anastomosis.¹ The tissue events can readily be visualised by ileocolonoscopy with biopsy in the months after surgery.

The presence of extensive lesions in the bowel, as visualised at endoscopy in the months after surgery, predicts rapid evolution to recurrent symptoms and eventually complications.

The behaviour of the disease (fibrotic versus perforating) tends to remain unchanged throughout the disease course and risk factors for early clinical recurrence are perforating behaviour, ileal or ileocolonic resection with ileocolonic anastomosis, and smoking.^{2,3}

True prophylactic therapy implies that the formation of new lesions, from early aphthous ulcers to full blown Crohn's disease, can be prevented using drug therapy. In that respect postsurgical prophylaxis is different from maintenance of medically induced remission of Crohn's disease as in the latter situation active lesions are still present in the bowel even though the patient does not experience the typical symptoms of the disease. Recently it has also become possible to heal the bowel medically using anti-tumour necrosis factor antibodies, but relapse after this therapy is accompanied by immediate (almost overnight) relapse of typical Crohn's lesions.

There are currently two strategies that seem to interrupt the natural history of Crohn's disease postoperatively—that is, treatment with nitroimidazol antibiotics and immunosuppression therapy using 6-mercaptopurine or azathioprine. Other current therapies of Crohn's disease have been rather disappointing.

Sulphasalazine or other 5-aminosalicylic acid (5-ASA) formulations have limited value in the prophylaxis of Crohn's disease recurrence. Meta-analysis of placebo controlled trials using 5-ASA formulations suggest a 20–30% reduction in the relative risk of recurrence (10% of the absolute risk) at 18–24 months with high doses of 5-ASA but demonstrate overlap with unity.^{4–7} Glucocorti-

costeroids, including the topically acting drug budesonide, are not effective.

Antibiotics are an attractive therapy as there is evidence that the commensal flora is involved in the perpetuation of inflammation in the bowel. In a placebo controlled trial⁸ it was shown that metronidazole 20 mg/kg for three months after resection with ileocolonic anastomosis significantly decreased the severity of recurrent lesions in the neoterminal ileum. This results in a delayed symptomatic recurrence. In a recent trial⁹ we confirmed the efficacy of nitroimidazol antibiotics as ornidazol 1 g/day for one year not only decreased the rate of endoscopic recurrences but this regimen also significantly diminished the clinical recurrence rate (9% v 33%). Again, however, the effect lasts only as long as the drug is maintained. The main drawback of this treatment is the poor tolerance of this antibiotic regimen with polyneuropathy on chronic use being the most disturbing side effect.

Another appealing therapy for postoperative recurrence prevention in Crohn's disease is immunosuppression with azathioprine. This drug has been shown to be effective in maintaining medically induced remission and can even heal severe postoperative recurrent disease.

There are only limited data on the use of immunosuppression for postoperative prophylaxis.

In a two year multicentre trial,¹⁰ 6-mercaptopurine 50 mg/day, mesalamine 3 g/day, and placebo were compared for postoperative maintenance of Crohn's disease remission. In this study 6-mercaptopurine was more effective than placebo. Clinical recurrence rates at 24 months amounted to 50% for 6-mercaptopurine, 59% for mesalamine, and 69% for placebo. Endoscopic recurrence rates were 68%, 77%, and 87% respectively.

The results of the latter study are somewhat disappointing in the sense that 6-mercaptopurine was less effective than expected. This is probably the consequence of the rather low dose of 50 mg of 6-mercaptopurine used where 1–1.5 mg/kg is the effective dose.

How should we then focus our therapeutic strategy? It is clear that a number of patients will not need postoperative prophylaxis as they will not suffer symptomatic recurrence because they either develop no new lesions or only limited tissue recurrence. The problem is that clinical risk factors for the development of clinical recurrence have not clearly been identified.

Therefore, we should focus on those patients who are identified as having developed important new Crohn's lesions in the remaining bowel as they will eventually develop symptomatic recurrence. With this aim we always carry out an ileocolonoscopy or barium follow through x rays in our patients in the clinical setting at six months after resection to identify those patients

P Rutgeerts
Internal Medicine, Division
of Gastroenterology,
University Hospital,
Gasthuisberg, Herestraat
49, B-3000 Leuven,
Belgium;
paul.rutgeerts@
uz.kuleuven.ac.be

Accepted for publication
17 September 2001

Summary

- Clinical recurrence of Crohn's disease after surgery is the consequence of early and evolutive recurrent lesions in the bowel.
- True prophylactic therapy prevents the development of these early "new" lesions.
- The most promising prophylactic therapies are early postoperative antibiotic therapy and immunosuppression.
- The optimal postoperative strategy involves endoscopic or radiologic studies of the bowel to identify those patients that have developed early recurrent lesions.

with clearcut recurrent lesions. These patients are candidates to receive 6-mercaptopurine or azathioprine. Induction of healing using anti-tumour necrosis factor strategies should be considered. Studies addressing the issue of postoperative recurrence prevention in Crohn's disease are greatly needed.

REFERENCES

- 1 Rutgeerts P, Geboes K, Vantrappen G, *et al.* Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990;**99**:956–63.
- 2 Lautenbach E, Berlin JA, Lichtenstein GR. Risk factors for early postoperative recurrence of Crohn's disease. *Gastroenterology* 1998;**115**:259–67.
- 3 Moskovitz D, McLeod RS, Greenberg GR, *et al.* Operative and environmental risk factors for recurrence of Crohn's disease. *Int J Colorectal Dis* 1999;**14**:224–6.
- 4 Caprilli R, Andreoli A, Capurso L, *et al.* 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.
- 5 McLeod RS, Wolff BG, Steinhart AH, *et al.* Prophylactic mesalamine treatment decreases postoperative recurrence of Crohn's disease. *Gastroenterology* 1995;**109**:404–13.
- 6 Brignola C, Cottone M, Pera A, *et al.* Mesalamine in the prevention of endoscopic recurrence after intestinal resection for Crohn's disease. Italian Cooperative Study Group. *Gastroenterology* 1995;**108**:345–9.
- 7 Lochs H, Mayer M, Fleig WE, *et al.* Prophylaxis of postoperative relapse in Crohn's disease with mesalamine: European Cooperative Crohn's Disease Study VI. *Gastroenterology* 2000;**118**:264–73.
- 8 Rutgeerts P, Hiele M, Geboes K, *et al.* Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection. *Gastroenterology* 1995;**108**:1617–21.
- 9 Rutgeerts PJ, D'Haens G, Baert F, *et al.* Nitroimidazole antibiotics are efficacious for prophylaxis of postoperative recurrence of Crohn's disease: A placebo controlled trial. *Gastroenterology* 1999;**116**:A808 (G3506).
- 10 Korelitz B, Hanauer S, Rutgeerts P, *et al.* Postoperative prophylaxis with 6MP, 5-ASA or placebo in Crohn's disease: a 2 year multicenter trial. *Gastroenterology* 1998;**114**:A688.

ANTAGONIST

Crohn's disease recurrence can be prevented after ileal resection

D S Rampton

About half of patients with ileal Crohn's disease have a clinical relapse within five years of a first resection; half will need a second operation by 10 years. The proposal that recurrence can be prevented is clearly untenable as there are no data whatsoever to indicate that any currently available measure can reduce to zero the postoperative relapse rate. However, I will take a less literal interpretation of the motion and review the evidence against the suggestion that the postoperative rate of symptomatic, as opposed to endoscopic, recurrence of ileal Crohn's¹ can be reduced by therapeutic interventions.

STOPPING SMOKING

There is strong retrospective data that stopping smoking halves the symptomatic recurrence rate up to 10 years after surgery.^{2,3} Furthermore, although not specifically relating to the postoperative course, a recent prospective trial has confirmed that stopping smoking improves the natural history of Crohn's.⁴

AMINOSALICYLATES

A meta-analysis⁵ covering four trials^{6–9} suggested that long term aminosaliclates slightly reduced the risk of symptomatic relapse after surgery (risk

reduction 13%, making the number of patients needing to be treated (NNT) to prevent one recurrence 8). However, a more recent placebo controlled European study¹⁰ showed no advantage for Pentasa (4 g/day) except in patients with localised ileal disease in whom the clinical relapse rate at 18 months was 22% on Pentasa and 40% on placebo. Furthermore, reassessment of the data analysed in Cammá's meta-analysis⁵ after inclusion of the European results,¹⁰ and exclusion of Caprilli's trial,⁶ which was not blinded or placebo controlled, decreased the risk reduction to only 8% (NNT 12%).¹¹ This NNT is probably too high to support use of aminosaliclates for postoperative prophylaxis except in the minority of patients with exclusively ileal disease.

NITROIMIDAZOLE ANTIBIOTICS

Oral metronidazole (400 mg three times daily for three months only) delayed symptomatic as well as endoscopic recurrence one year after surgery but the clinical advantage over placebo was lost beyond that period.¹² Furthermore, the side effects of metronidazole make it an unattractive agent for widespread or long term use. Preliminary data suggest a beneficial effect for a better tolerated nitroimidazole, ornidazole (1 g/day for a

Debate

D S Rampton

Academic Department of Adult and Paediatric Gastroenterology, St Bartholomew's and the Royal London School of Medicine and Dentistry, London, UK

Correspondence to: Dr DS Rampton, Endoscopy Unit, Basement, Royal London Hospital, London E1 1BB, UK; drampton@mds.qmw.ac.uk

Accepted for publication 17 September 2001

Debate

year), on endoscopic recurrence but information on clinical relapse is not yet available.¹³

BUDESONIDE

Controlled ileal release budesonide (6 mg/day) halved the postoperative endoscopic recurrence rate at one year for inflammatory but not fibrostenotic Crohn's, but clinical relapses were as common as in placebo treated patients.¹⁴

THIOPURINES

In a preliminary study, low dose 6-mercaptopurine (50 mg/day) was better than placebo and aminosalicylates in preventing symptomatic, endoscopic, and radiological recurrence after surgery.¹⁵ However, the placebo relapse rate was 70% at two years, and a recurrence rate of 53% for patients given 6-mercaptopurine scarcely represents a ringing endorsement of this treatment, particularly in view of its potential side effects. Thiopurines need further evaluation, at full dose, for postoperative prophylaxis.

THE FUTURE

Interleukin 10 was no better than placebo in preventing postoperative endoscopic or clinical relapse at one year in a recent study¹⁶ but trials of other biological therapies, including infliximab, antibiotics and probiotics, a liquid formula diet, and other immunomodulatory approaches such as fish oil¹⁷ would be of interest. Such studies should be stratified for operation type and phenotypic and even genotypic risk factors, and include longer follow up than hitherto.¹⁸

CONCLUSIONS

Apart from stopping smoking, no therapeutic measure can be unreservedly recommended for routine prophylaxis after ileal resection for Crohn's. Although colonoscopy at, say, six months after surgery might be used to select patients, according to the severity of endoscopic recurrence,¹ for specific therapies, the validity of this approach needs confirmation in further clinical trials.

Having been instructed by the editor to be deliberately negative about existing data, I shall end by stating what I actually do. Smokers are urged to stop. A discussion with the immediately postoperative patient about the available pharmacological evidence is often concluded by patients with uncomplicated disease indicating their enthusiasm to be off all tablets after months or years of such treatment. Patients with exclusively ileal disease are advised however to use Pentasa (4 g/day).¹⁰ Those with aggressive, perforating, or extensive disease, or a second or later resection, are advised to take (and in many instances of course continue on) a thiopurine in full dose, despite the lack of data to support this approach. Sadly, I am unable to reassure patients that any drug will substantially reduce their chances of symptomatic recurrence after ileal surgery.

REFERENCES

- 1 Rutgeerts P, Geboes K, van Trappen G, et al. Predictability of the post-operative course of Crohn's disease. *Gastroenterology* 1990;**99**:950-63.
- 2 Sutherland LR, Ramcharan S, Bryant H, et al. Effect of cigarette smoking on recurrence of Crohn's disease. *Gastroenterology* 1990;**98**:1123-8.

Summary

- Recurrence of Crohn's disease after ileal resection cannot yet be prevented.
- Stopping smoking may decrease recurrence rate but prospective studies are lacking.
- Aminosalicylates reduce the risk of clinical recurrence after resection of exclusively small bowel disease, but their prophylactic efficacy in most patients with Crohn's is marginal.
- Nitroimidazole antibiotics, budesonide, and 6-mercaptopurine have been shown to reduce postoperative endoscopic recurrence rates, but none has yet been shown to have sufficient effect on the clinical relapse rate to be recommended routinely for long term prophylaxis.
- There is a need for further trials of immunomodulatory agents, antibiotics, and probiotics for postoperative prophylaxis of Crohn's disease.

- 3 Cottone M, Rosselli M, Orlando A, et al. Smoking habits and recurrence in Crohn's disease. *Gastroenterology* 1994;**106**:643-8.
- 4 Cosnes J, Beaugerie L, Carbonnel F, et al. Smoking cessation and the course of Crohn's disease: an intervention study. *Gastroenterology* 2001;**120**:1093-1099.
- 5 Cammá C, Giunta M, Roselli M, et al. Mesalamine in the maintenance treatment of Crohn's disease: a meta-analysis adjusted for confounding variables. *Gastroenterology* 1997;**113**:1465-73.
- 6 Caprilli R, Andreoli A, Capurso L, et al. Oral mesalazine (5-aminosalicylic acid; Asacol) for the prevention of post-operative recurrence of Crohn's disease. *Aliment Pharmacol Ther* 1994;**8**:35-43.
- 7 McLeod RS, Wolff BG, Steinhardt AH, et al. Prophylactic mesalamine treatment decreases post-operative recurrence of Crohn's disease. *Gastroenterology* 1995;**109**:404-13.
- 8 Brignola C, Cottone M, Pera A, et al. Mesalamine in the prevention of endoscopic recurrence after intestinal resection for Crohn's disease. *Gastroenterology* 1995;**108**:345-9.
- 9 Sutherland LR, Martin F, Bailey RG, et al. A randomised, placebo-controlled, double-blind trial of mesalamine in the maintenance of remission in Crohn's disease. *Gastroenterology* 1997;**112**:1069-77.
- 10 Lochs H, Mayer M, Fleig WE, et al. Prophylaxis of post-operative relapse in Crohn's disease with mesalamine: European Co-operative Crohn's Disease Study VI. *Gastroenterology* 2000;**118**:264-73.
- 11 Sutherland LR. Mesalamine for the prevention of post-operative recurrence: is nearly there the same as being there? *Gastroenterology* 2000;**118**:436-8.
- 12 Rutgeerts P, Hiele M, Geboes K, et al. Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection. *Gastroenterology* 1995;**108**:1617-21.
- 13 Rutgeerts PJ, D'Haens G, Baert F, et al. Nitroimidazole antibiotics are efficacious for prophylaxis of post-operative recurrence of Crohn's disease: a placebo-controlled trial. *Gastroenterology* 1999;**116**:A808.
- 14 Hellers G, Cortot A, Jewell DP, et al. Oral budesonide for prevention of recurrence following ileocaecal resection of Crohn's disease: a one-year placebo-controlled study. *Gastroenterology* 1999;**116**:294-300.
- 15 Korelitz B, Hanauer S, Rutgeerts P, et al. Post-operative prophylaxis with 6-MP, 5-ASA or placebo in Crohn's disease: a two year multi-centre trial. *Gastroenterology* 1998;**114**:A1011.
- 16 Colombel J-F, Rutgeerts P, Malchow H, et al. Interleukin-10 (Tenovil) in the prevention of post-operative recurrence of Crohn's disease. *Gut* 2000;**49**:42-6.
- 17 Belluzzi A, Brignola C, Campieri M, et al. Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease. *N Engl J Med* 1996;**334**:1517-60.
- 18 Present DH. The prevention of Crohn's disease after surgery: metronidazole is a small but continuous medical advancement. *Gastroenterology* 1995;**108**:1935-4.