Debate

ANTAGONIST

Early surgical intervention in ulcerative colitis

M A Kamm

Medical treatment for both fulminant and chronic active colitis is now usually very effective. Given that surgical therapy is associated with substantial morbidity and mortality, the preferred treatment should be conservative.

FULMINANT ULCERATIVE COLITIS

Intravenous cyclosporin is of proven value in managing fulminant ulcerative colitis. In the definitive study of patients who failed intravenous steroid therapy, nine of 11 patients responded to cyclosporin compared with none of nine patients on placebo.[1] Open clinical use has confirmed that colectomy can be avoided in the majority of patients.[2–4] with short term response rates of up to 86%.[4]

Cyclosporin can be continued even if there is mild colonic dilatation, provided the patient is clinically improving.[4] Continued close observation by a gastroenterologist and a surgeon is essential.

Criticism of cyclosporin has centred on drug toxicity, possible compromise of surgical outcome if drug therapy fails, and the possibility that successful drug therapy only delays inevitable surgery.

The original trial dose of cyclosporin was 4 mg/kg/day intravenously,[1] a dose associated with considerable morbidity. We[5] and others[6] have used a dose of 2 mg/kg/day, without concomitant steroids, for nine years without significant morbidity. We treated 31 patients with low dose intravenous cyclosporin, usually without concomitant steroids. Colectomy was avoided in 77% of patients in the short term and 45% in the long term.[5] A recent randomised trial has demonstrated equivalent efficacy between low and higher dose regimens.[7]

Several series have now demonstrated that if cyclosporin therapy fails, the results of colectomy are not compromised.

The introduction of azathioprine or 6-mercaptopurine (6-MP) immediately after successful cyclosporin therapy is the key to maintaining remission. In one study of 36 acute responders, subsequent colectomy was performed in 20% of patients on 6-MP compared with 45% not on 6-MP.[4]

In the long term, up to 80% of responders to acute cyclosporin who are maintained on azathioprine or 6-MP avoid colectomy.[4]

The minimal morbidity of low dose monotherapy intravenous cyclosporin, followed by maintenance azathioprine therapy, stands in marked contrast with the morbidity and mortality associated with colectomy for acute disease. For acute disease without perforation, the major complication rate of colectomy is 40–50%,[8 9] and the mortality rate 3%[10] to 7%.[9]

LONG TERM RESULTS OF SURGERY

All operations are associated with long term morbidity in a significant proportion of patients.

After 20 years, the cumulative incidence of stoma complications is 76%.[11] Complications include stoma revision (28%), skin problems (34%), intestinal obstruction (23%), retraction (17%), and parastomal herniation (16%). Stomas also carry a psychological, physical, and financial burden.

Patients with an ileorectal anastomosis have an increased bowel frequency, and still require continued rectal cancer surveillance.

Patients undergoing a restorative proctocolectomy (pouch) procedure usually require multiple operations. Half experience substantial perioperative morbidity. In the longer term, the cumulative risk for pouchitis is 51% at four years.[12] Pouch excision at five years occurs in 15–20% of patients.[13] Even if the pouch functions well, without substantial complications, bowel function is still inferior to the unoperated patient in remission.

These complications of surgery are acceptable if colectomy was unavoidable, due to uncontrollable disease, incipient perforation, or cancer. Under other circumstances the price seems high.

LONG TERM DISEASE CONTROL

In the majority of patients it is possible to maintain remission. 5-Amino salicylic acid (5-ASA) therapy reduces the annual relapse rate from 73% to 21%.[14 15]

In those who relapse despite 5-ASA, azathioprine or 6-MP maintain remission in most patients.[15] Upward dose titration in patients without disease control at a standard dose will usually achieve remission.[16] Approximately 10–15% of patients will not tolerate azathioprine or 6-MP. The only other major limitation is the development of leucopenia in 4% of patients treated with the standard dose of 2 mg/kg/day.[17] Azathioprine does not increase the risk of developing colonic or other cancer.[18]

Colectomy should only rarely be necessary for uncontrolled disease.

CANCER RISK

In some centres the colorectal cancer rate in colitics is no different to that of the general population.[19] Although this may relate to a high colectomy rate, other factors such as good compliance with 5-ASA medication may be important.[19] No account has been taken of the

Correspondence to:
M A Kamm, Department of Gastroenterology, St Mark's Hospital, Watford Rd, Harrow HA1 3UJ, UK; kamm@ic.ac.uk

Accepted for publication 8 July 2003

Debate

Summary points

- Intravenous low dose cyclosporin heals fulminant colitis in most patients with low morbidity.
- After avoiding colectomy with cyclosporin, remission should be maintained with azathioprine or 6-MP.
- Chronic active disease can usually be effectively managed by increasing the dose of azathioprine or 6-MP.
- The morbidity and mortality of colectomy and of a stoma or restorative surgery should be considered when discussing treatment options.
- Surgery is indicated for high grade dysplasia or cancer, imminent perforation despite maximal treatment, or chronic active disease despite maximal treatment.

morbidity and mortality from colectomy in these populations.[19]

The real comparison of morbidity and mortality from all causes, in operated and unoperated patients, has not been made. Colectomy to prevent cancer cannot, therefore, be recommended on these grounds.

Patients with definite high grade dysplasia, a mass lesion associated with definite dysplasia, and cancer should undergo surgery.

Debate surrounds the correct management of low or intermediate grade dysplasia. This relates to the lack of uniform diagnosis between pathologists, and the uncertain natural history of low grade dysplasia. Colectomy, with its attendant morbidity and mortality, is unwarranted, unless there are associated poor prognostic features.[20]

CONCLUSION

Surgery is justified for cancer or high grade dysplasia, imminent perforation despite maximal drug therapy, and uncontrolled chronic active disease, despite maximal immunosuppressive therapy. Under other circumstances the patient is best advised to keep their colon.

REFERENCES

1 **Lichtiger S**, Present DH, Kornbluth A, *et al*. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994;**330**:1841–5.
2 **Hyde GM**, Thillainayagam AV, Jewell DP. Intravenous cyclosporin as rescue therapy in severe ulcerative colitis: time for a reappraisal? *Eur J Gastroenterol Hepatol* 1998;**10**:411–13.
3 **Stack WA**, Long RG, Hawkey CJ. Short- and long-term outcome of patients treated with cyclosporin for severe acute ulcerative colitis. *Aliment Pharmacol Ther* 1998;**12**:973–8.
4 **Cohen RD**, Stein R, Hanauer SB. Intravenous cyclosporin in ulcerative colitis: a five-year experience. *Am J Gastroenterol* 1999;**94**:1587–92.
5 **Rayner CK**, McCormack G, Emmanuel AV, *et al*. Long term results of low dose intravenous cyclosporin for acute severe ulcerative colitis. *Aliment Pharmacol Ther* 2003;**18**:303–8.
6 **Actis GC**, Ottobrelli A, Pera A, *et al*. Continuously infused cyclosporine at low dose is sufficient to avoid emergency colectomy in acute attacks of ulcerative colitis without the need for high-dose steroids. *J Clin Gastroenterol* 1993;**17**:10–13.
7 **van Assche G**, D'Haens G, Noman M, *et al*. Randomised double blind comparison of 4 mg/kg versus 2 mg/kg IV cyclosporine in severe ulcerative colitis. *Gastroenterology* 2002;**122**:A81.
8 **Leijonmarck CE**, Brostrom O, Monsen U, *et al*. Surgical treatment of ulcerative colitis in Stockholm County, 1955 to 1984. *Dis Colon Rectum* 1989;**32**:918–26.
9 **Albrechtsen D**, Bergan A, Mygaard K, *et al*. Urgent surgrey for ulcerative colitis: early colectomy in 132 patients. *World J Surg* 1981;**5**:607–15.
10 **Hawley PR**. Emergency surgery for ulcerative colitis. *World J Surg* 1988;**12**:169–73.
11 **Leong AP**, Londono-Schimmer EE, Phillips RK. Life-table analysis of stomal complications following ileostomy. *Br J Surg* 1994;**81**:727–9.
12 **Stahlberg D**, Gullberg K, Liljeqvist L, *et al*. Pouchitis following pelvic pouch operation for ulcerative colitis. Incidence, cumulative risk, and risk factors. *Dis Colon Rectum* 1996;**39**:1012–18.
13 **Korsgen S**, Keighley MR. Causes of failure and life expectancy of the ileoanal pouch. *Int J Colorectal Dis* 1997;**12**:4–8.
14 **Misiewicz JJ**, Lennard-Jones JE, Connell AM, *et al*. Controlled trial of sulphasalazine in maintenance therapy for ulcerative colitis. *Lancet* 1965;**1**:185–8.
15 **Kamm MA**. Maintenance of remission in ulcerative colitis. *Aliment Pharmacol Ther* 2002;**16**(suppl 4):21–4.
16 **Barbe L**, Marteau P, Lemann M, *et al*. Dose raising of azathioprine beyond 2.5mg/kg/day in Crohn's disease patients who fail to respond to a standard dose. *Gastroenterology* 1998;**114**:A925.
17 **Connell W**, Kamm MA, Lennard-Jones JE, *et al*. Bone marrow toxicity from azathioprine: twenty-seven year experience in inflammatory bowel disease. *Gut* 1993;**34**:1081–5.
18 **Connell WR**, Kinlen LJ, Ritchie JK, *et al*. Long term risk of neoplasia in patients treated with azathioprine for inflammatory bowel disease. *Lancet* 1994;**343**:1249–52.
19 **Langholz E**, Munkholm P, Davidsen M, *et al*. Colorectal cancer risk and mortality in patients with ulcerative colitis. *Gastroenterology* 1992;**103**:1444–51.
20 **Ullman TA**, Loftus EV jr, Kakar S, *et al*. The fate of low grade dysplasia in ulcerative colitis. *Am J Gastroenterol* 2002;**97**:922–7.