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Lecture

Post-Operative Management of Ulcerative Colitis and Crohn's Disease

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INTRODUCTION

The post-operative management of ulcerative colitis (UC) and Crohn's disease (CD) is a complicated and life-long issue. For UC this means essentially the management of pouchitis, since most colectomized patients undergo an ileal pouch with anal anastomosis (IPAA), whereas for CD this implies the identification of predictors of recurrence and its prevention and treatment.

ULCERATIVE COLITIS

The colectomy rate in UC has fallen somewhat but remains substantial. Recent data from the European collaborative study of inflammatory bowel disease (EC-IBD) revealed colectomy rates of 10.4% in northern Europe and 3.9% in southern Europe, for a pan-European rate of 8.7% at 10 years of follow-up.[1] Pouchitis is present in 50% of patients by as little as three years after pouch creation.[2] The diagnosis is established by endoscopy and histology, and antibiotics are in the forefront of treatment.

The etiology of pouchitis is enigmatic and likely related to whatever causes UC; it does not occur after surgery for other colonic diseases. Predictors of pouchitis include extensive colitis, severe colitis, young age at onset of colitis, female gender, backwash ileitis, extra-intestinal manifestations, primary sclerosing cholangitis, pANCA positive patients and non-smoking patients.[2] A number of these factors are disputed in various publications. Experimentally, individuals with increased colonic mucosal permeability to bacteria are at risk. Indeterminate colitis patients more prone to develop pouchitis after IPAA than UC patients, and the pouchitis is generally worse than that after surgery for UC. Pouchitis has been classified to simplify the clinical approach to management.[3] Disease activity is graded as mild, moderate and severe. Disease behavior in 90% of cases is an acute illness of less than 4 weeks duration, which however may recur, whereas in 10% it is chronic and lasts 4 weeks or more, with some individuals in this group being refractory to all medical treatments. The symptoms of pouchitis include diarrhea, liquid stools, fecal incompetence, abdominal cramps, urgency or tenesmus, rectal bleeding, fever and extra-intestinal manifestations as seen in UC.[4] The endoscopic examination includes taking biopsies from sites of acute inflammation as well as from normal looking pouches. It is important to look for cuffitis in the rectal cuff. However, a few ulcers at the staple line alone do not imply pouchitis.

There is a differential diagnosis of pouchitis, which includes adenocarcinoma, CD, infectious colitis (*Clostridium difficile*, Cytomegalovirus) and ischemia. 10-15% of UC patients undergoing ileal pouch with anal anasto-

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Abbreviations

UC = *ulcerative colitis*
CD = *Crohn's disease*
IPAA = *ileal pouch with anal anastomosis*
EC-IBD = *European collaborative study of inflammatory bowel disease*

mosis were reported to eventually have a change of diagnosis to CD. Warning signs are the presence of fistula or stricture.

The available treatments for pouchitis are listed in the Table. Antibiotics are indicated in post-UC pouchitis. Metronidazole 400 mg thrice daily for 2 weeks is probably the commonest antibiotic in use in pouchitis, but there is evidence that ciprofloxacin 250 mg twice daily for 2 weeks is better.[5] Advantages of ciprofloxacin include its efficacy where metronidazole has failed, its better tolerance and its suitability for prolonged therapy in reduced dosage. Combination antibiotic therapy remains an option. In antibiotic resistant subjects corticosteroids, budesonide and immunomodulators can all be used, generally in the order shown. Cyclosporine could perhaps be tried in selected cases. The role of probiotics (such as VSL#3) is unproven. The efficacy of infliximab in UC has now been confirmed in two large trials.[6] Infliximab will likely become a candidate treatment in resistant pouchitis. Other biologic agents under investigation may be tried in resistant pouchitis in the near future. As a last resort when all medical therapy has failed the pouch must be taken down, leaving the patient with a permanent ileostomy. Cigarette smoking may prevent pouchitis, but should probably not be advised to patients. Pouch surveillance by periodic endoscopy is indicated where UC was complicated by carcinoma.

CROHN'S DISEASE

In the EC-IBD Crohn's disease cohort over one quarter of patients underwent at least one surgical intervention during the first ten years after diagnosis. At 1, 5 and 10 years of follow-up, the surgical rates were 7.1%, 21.2% and 28.9%.[7] Bowel resection, stricturoplasty and surgery for fistula were the main operations performed. Ileal pouch surgery remains contraindicated in CD. Each operated CD patient can be regarded as undergoing (temporary) transition to a remission state; many will have recurrent surgeries and transitions. The duration of remission is calculated as some 500 days in 50% of operated cases (range for all cases was 200 to 800 days; differences existed between patients in north and south Europe).[7] Patients with the NOD2/CARD15 Gly908Arg mutation or ASCA are more likely to require surgery.[8]

Table. Treatment of pouchitis

Clinical condition	Treatment
Post-UC pouchitis	Antibiotics, corticosteroids, immunomodulators, infliximab
Crohn's disease	As for Crohn's disease elsewhere
Cytomegalovirus	Gancyclovir
Clostridium difficile	Vancomycin
Ischemia with stricture	Endoscopic dilatation
Cuffitis	Mesalazine, corticosteroids
Irritable pouch syndrome	Anti-spasmodic medications

In a Canadian study disease recurrence was shown to begin very early in post-surgical CD patients; recurrence was observed in 6%, 14% and 22% of subjects by 1, 2 and 3 years after initial surgery.[9] Pre-operative predictors of recurrence after surgery are smoking, short duration of disease before surgery, penetrating disease, disease limited to the colon, jejunal site of disease, ileo-colonic disease and NOD2/CARD15 gene variants.[10-13] Post-operative predictors of recurrence include endoscopic lesions detected after surgery, discontinuation of mesalazine,[14] discontinuation of 6-mercaptopurine,[7,9,10] and length of post-surgical follow-up.[14] Non-predictors of recurrence were age, sex, family history of CD, disease duration prior to surgery, length of resected bowel, granulomas in resected specimen, blood transfusions, presence of complications after surgery and the C-reactive protein level.

Several modalities are available for the detection of recurrence in CD patients. The earliest evidence comes from enteroscopy: endoscopic signs of recurrence are present in 63% of patients at 2 years after surgery. Enteroscopy will probably be replaced by video-capsule endoscopy in the near future. It would seem prudent to carry out video-capsule endoscopy early in the post-operative disease course in all patients without strictures in the bowel. Radiology is a less accurate technique.

There remains no standard of therapy for preventing post-operative recurrence. Prophylaxis however should be aggressive. The correct time to start therapy is from the post-operative period. Treatment with corticosteroids or budesonide does not prevent recurrence. The nitroimidazole antibiotics metronidazole and ornidazole can prevent early endoscopic recurrence and postpone symptomatic relapse but are not well tolerated. Mesalazine is to date the most investigated drug in post-surgical CD. Mesalazine prevented post-operative recurrence in a large meta-analysis of 15 placebo-controlled trials performed in 1988-97 and involving 2097 patients.[15] The rate of side-effects was 14%, the same as for placebo. The end-point "clinical relapse" favored mesalazine, with overall risk difference from placebo being -6.3% ($P<0.003$) and number-to-treat was 10. Four of these trials concerned surgical remission with mesalazine; again, the cumulative risk difference favored mesalazine. A subsequent dose-finding study showed no difference of efficacy between 4.0 and 2.4 grams of mesalazine daily.[16] A prospective open-label study of 142 CD post-operative patients showed no difference for clinical or

surgical relapse between azathioprine 2mg/kg/day and mesalazine 3g/day over a 24 month follow-up interval.[12] In a sub-group with "previous bowel resection" the Odds Ratio of 4.8 (CI 1.5-15.8) favored azathioprine. A further trial examined the prevention of post-operative recurrence in 131 CD patients recruited in 1992-6, using 6-mercaptopurine 50 mg/day, mesalazine 3g/day and placebo.[17] 6-Mercaptopurine but not mesalazine was more effective than placebo by survival analysis ($P<0.05$) for recurrence by clinical (50%) and mild-moderate endoscopic (43%) end-points over 800 days of follow-up. The rather high rates of relapse with 6-mercaptopurine were likely the consequence of using too low a dose of this drug. The studies by Ardizonne et al.[12] and Hanauer et al.[17] would seem to indicate that mesalazine is only 10% more effective than placebo and purine metabolites are only 10% more effective than mesalazine.[18] In a withdrawal trial of azathioprine 83 patients in remission on azathioprine for more than 42 months were randomized to continued azathioprine or placebo for a further period of 18 months. The hypothesis that azathioprine continuation was superior to azathioprine withdrawal was not rejected ($P=0.2$, mean relapse rate 7.9% vs. 21.3%).[19] Multivariate analysis detected three independent factors which were associated with a higher relapse rate: C-reactive protein ≥20 mg, hemoglobin <12 grams, and time without steroids ≥50 months. Toxic effects will always limit the use of thiopurines, but the need for TMPT measurements before treatment with thiopurines is still not clear-cut.[20] Methotrexate is of limited use in CD patients.

The efficacy of infliximab in prolonging post-operative remission requires formal investigation. At present the issue has to be approached by examining the use of infliximab in CD patients in general. The ACCENT I trial studied the efficacy of infliximab as maintenance treatment for CD, where 335 responders to infliximab 5 mg/kg were divided into 3 groups: placebo, infliximab 5 mg/kg, and infliximab 10 mg/kg, with the end-point based on the Crohn's Disease Activity Index.[21] Patients who responded to an initial dose of infliximab were more likely to be in remission at weeks 30 and 54, to discontinue corticosteroids, and to maintain their response for a longer period of time, when infliximab treatment was scheduled to be administered every 8 weeks instead of "on demand." In the scheduled treatment patients of ACCENT I there were fewer CD-related hospitalizations ($P<0.02$), fewer surgeries ($P<0.01$), a better rate of mucosal healing ($P<0.05$), improved quality of life, a lower rate of developing antibodies to infliximab, and no increase of side-effects.[22] A recent Danish analysis of the results with infliximab treatment in CD over 12 months showed that 40% of patients were prolonged responders, 24% developed drug dependence, and 36% were non-responders.[23] Of the newer biologic drugs undergoing clinical trials adalimumab, a self-injectable human IgG1 monoclonal antibody to TNF, has shown promising results over placebo in two 4 week follow-up studies[24,25] and a one year trial[26] in moderate to severe CD.

CONCLUSIONS

The post-operative management of UC and CD is a challenge. It is clear that a better approach to prophylactic therapy in post-surgical UC and CD patients is an urgent issue. For the former it seems that better antibiotic therapy is needed. For both diseases the future appears to lie in the realm of biologic therapies.

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