Prevention of Postoperative Recurrence in Crohn's Disease

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I read with great interest the review by Vuitton et al. [1]. The authors identified the following five parameters as established predictors for postoperative recurrence in Crohn's disease (CD): smoking, prior intestinal resection, penetrating behaviour, perianal disease, and extensive small bowel resection (>50 cm). However, these risk factors are of limited value in clinical practice since it is difficult to make a precise assessment of risk for recurrence with these parameters in an individual patient. A more practical predictor has been considered to be the severity of endoscopic inflammation in the early postoperative period [2]. In a prospective cohort study, we found a significant positive correlation between the endoscopic severity of the proximal site of the ileocolonic anastomosis at 6 months after resection and the clinical recurrence rate during the following 5 years [3]. The assessment of endoscopic lesions at the proximal site of the anastomosis appeared to be valuable for predicting clinical recurrence after ileocolonic resection for CD.

The authors proposed a treatment algorithm for the prevention of postoperative recurrence based on risk stratification [1]. As stated above, smoking, prior intestinal resection, penetrating behaviour, perianal disease, and extensive small bowel resection (>50 cm) are identified as risk factors for postoperative recurrence. In their algorithm, patients with none of these risk factors need no treatment, patients with one risk factor are treated with thiopurine $\pm$ metronidazole, and patients with ≥ 2 risk factors are treated with anti-tumour necrosis factor (TNF) agents. This means that patients are classified into three groups with

low, moderate and high risk for recurrence according to clinical parameters identified at the time of operation. However, there is no rigorous evidence to divide patients into these three groups depending on the number of risk factors for postoperative recurrence: 0, 1 and ≥ 2 . I do feel that the significance of each parameter as a risk factor for recurrence is quite different. Risk factors identified in a meta-analysis are smoking [4] and penetrating behaviour [5]. Smokers have a 2.5-fold increased risk of surgical recurrence and a two-fold risk of clinical recurrence compared with non-smokers [4]. Patients with penetrating disease had an increased risk of recurrence compared with those with non-penetrating disease (hazard ratio = 1.50) [5]. The most significant risk factor is considered to be smoking. Penetrating behaviour is also a significant risk factor. However, the significance of the other parameters such as prior intestinal resection, perianal disease, and extensive small bowel resection is controversial based on the results of previous trials [6]. Further investigation on this issue is needed.

In their algorithm, ileocolonoscopy is conducted at 6 months after surgery. In patients with a Rutgeerts score ≥ 1 [2], the treatment should be stepped up. This recommendation may be based on the evidence obtained in previous trials. Two prospective studies investigated the effects of an anti-TNF agent (infliximab) on early endoscopic lesions (Rutgeerts score ≥ 2) at 6 months after ileocolonic resection for CD [7, 8]. Infliximab therapy significantly improved endoscopic inflammation and reduced the risk of subsequent clinical recurrence. In contrast, recent randomized controlled trials (RCTs) found that anti-TNF therapy with infliximab or adalimumab initiated soon after surgery was useful in preventing postoperative recurrence in CD [9–11]. Should we start anti-TNF therapy soon after surgery or after confirming early

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endoscopic recurrence? Further investigation is necessary. However, I do believe that anti-TNF therapy should be used for selective patients at a high risk of recurrence. All postoperative patients do not have to receive anti-TNF therapy because of potential serious adverse events (infection and malignancy) and high treatment costs. It is reasonable to start anti-TNF therapy in patients who develop early endoscopic recurrence at 6 months after resection for CD. The following issues should also be clarified in the management of postoperative CD with anti-TNF therapy:

- How long should anti-TNF therapy be continued once it is started?
- Which anti-TNF agent—infliximab or adalimumab—should be used as a first- and second-line treatment?
- Whether concomitant immunosuppressants enhance the efficacy of anti-TNF agents?

Their algorithm for prevention of postoperative recurrence should be indicated for patients who have resection for localized ileocolonic CD [1]. In clinical practice, many patients need concomitant small bowel resection or strictureplasty for active disease at the time of ileocolonic resection for CD. Among patients with more proximal small bowel CD in whom the anastomosis is unreachable via conventional ileocolonoscopy, a different strategy is necessary. Monitoring using new imaging techniques and biomarkers may be required for such patients. Transabdominal ultrasound, magnetic resonance enterography and small bowel capsule endoscopy are less invasive diagnostic methods emerging as alternative approaches for identifying postoperative CD recurrence in the small bowel [12]. The value of these imaging techniques in postoperative CD should be further investigated. In our recent study, both fecal calprotectin and lactoferrin levels correlated well with endoscopic activity after ileocolonic resection for CD [13]. Fecal calprotectin and lactoferrin may be clinically relevant biomarkers for predicting postoperative recurrence. Further trials should strengthen the findings of our investigation.

In conclusion, further studies are necessary to establish criteria for recurrence risk assessment and prophylactic treatment strategy in the management of postoperative CD. At the moment, endoscopic monitoring and treatment step-up should be important therapeutic strategies for the prevention of postoperative recurrence in CD. Furthermore, to evaluate the effects of anti-TNF agents for the prevention

and treatment of postoperative recurrence in CD, further large RCTs are necessary.

Conflict of interest None to declare.

References

1. Vuitton L, Koch S, Peyrin-Biroulet L. Preventing postoperative recurrence in Crohn's disease: what does the future hold? *Drugs*. 2013;73:1749–59.
2. Rutgeerts P, Geboes K, Vantrappen G, et al. Predictability of the postoperative course of Crohn's disease. *Gastroenterology*. 1990;99:956–63.
3. Yamamoto T, Bamba T, Umegae S, et al. The impact of early endoscopic lesions on the clinical course of patients following ileocolonic resection for Crohn's disease: a 5-year prospective cohort study. *United Eur Gastroenterol J*. 2013;1:294–8.
4. Reese GE, Nanidis T, Borysiewicz C, et al. The effect of smoking after surgery for Crohn's disease: a meta-analysis of observational studies. *Int J Colorectal Dis*. 2008;23:1213–21.
5. Simillis C, Yamamoto T, Reese GE, et al. A meta-analysis comparing incidence of recurrence and indication for reoperation after surgery for perforating versus nonperforating Crohn's disease. *Am J Gastroenterol*. 2008;103:196–205.
6. Yamamoto T, Watanabe T. Strategies for the prevention of postoperative recurrence of Crohn's disease. *Colorectal Dis*. 2013;15:1471–80.
7. Yamamoto T, Umegae S, Matsumoto K. Impact of infliximab therapy after early endoscopic recurrence following ileocolonic resection of Crohn's disease: a prospective pilot study. *Inflamm Bowel Dis*. 2009;15:1460–6.
8. Sorrentino D, Terrosu G, Paviotti A, et al. Early diagnosis and treatment of postoperative endoscopic recurrence of Crohn's disease: partial benefit by infliximab—a pilot study. *Dig Dis Sci*. 2012;57:1341–8.
9. Regueiro M, Schraut W, Baidoo L, et al. Infliximab prevents Crohn's disease recurrence after ileal resection. *Gastroenterology*. 2009;136:441–50.
10. Yoshida K, Fukunaga K, Ikeuchi H, et al. Scheduled infliximab monotherapy to prevent recurrence of Crohn's disease following ileocolic or ileal resection: a 3-year prospective randomized open trial. *Inflamm Bowel Dis*. 2012;18:1617–23.
11. Savarino E, Bodini G, Dulbecco P, et al. Adalimumab is more effective than azathioprine and mesalamine at preventing postoperative recurrence of Crohn's disease: a randomized controlled trial. *Am J Gastroenterol*. 2013;108:1731–42.
12. Van Assche G, Dignass A, Reinisch W, et al.; European Crohn's and Colitis Organisation (ECCO). The second European evidence-based consensus on the diagnosis and management of Crohn's disease: special situations. *J Crohns Colitis*. 2010;4: 63–101.
13. Yamamoto T, Shiraki M, Bamba T, et al. Faecal calprotectin and lactoferrin as markers for monitoring disease activity and predicting clinical recurrence in patients with Crohn's disease after ileocolonic resection: a prospective pilot study. *United Eur Gastroenterol J*. 2013;1:368–74.