

# CASE STUDY SERIES IN IBD

## Case Report: Managing Postoperative Crohn's Disease

Jurij Hanzel, MD, PhD,<sup>1,2</sup> Sudheer Kumar Vuyyuru, DM,<sup>2,3</sup> Neeraj Narula, MD, MPH,<sup>4</sup> Christopher Ma, MD, MPH,<sup>2,5</sup> Brian G. Feagan, MD,<sup>2,3,6</sup> and Vipul Jairath, MD, PhD<sup>2,3,6</sup>

<sup>1</sup>Faculty of Medicine, University of Ljubljana and Department of Gastroenterology, University Medical Center Ljubljana, Ljubljana, Slovenia

<sup>2</sup>Alimentiv, London, Ontario, Canada

<sup>3</sup>Division of Gastroenterology, Department of Medicine, Western University, London, Ontario, Canada

<sup>4</sup>Division of Gastroenterology, Department of Medicine and Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, Ontario, Canada

<sup>5</sup>Division of Gastroenterology & Hepatology, Departments of Medicine and Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

<sup>6</sup>Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada

**A** 31-year-old male patient presented 3 years ago with right lower quadrant pain, increased stool frequency, and weight loss of 10 pounds. He smoked 1 pack of cigarettes each day. On presentation, he had anemia (hemoglobin, 108 g/L), hypoalbuminemia (serum albumin, 30 g/L), and elevated C-reactive protein (CRP) (40 mg/L). Ileocolonoscopy revealed multiple serpiginous longitudinal ulcers in the cecum and terminal ileum, consistent with Crohn's disease (CD). Histopathology showed chronic active inflammation, crypt architectural distortion, and occasional granulomas. Computed tomography (CT) enterography showed long (15 cm) segment thickening with mural stratification involving the terminal ileum, cecum, and ascending colon with no evidence of upstream dilatation, all consistent with a diagnosis of CD. Treatment was initiated with oral corticosteroids and azathioprine simultaneously. His symptoms improved, and corticosteroids were tapered over 2 months; azathioprine (2.5 mg/kg) was continued.

He was free of symptoms for 6 months, but then presented to the emergency department with acute abdominal pain, distension, and vomiting. CT of the abdomen showed evidence of intestinal obstruction with a transition point at the terminal ileum, proximally dilated small bowel loops with air-fluid levels, and adherent bowel loops in the right lower quadrant forming an early inflammatory mass. Blood investigations showed anemia (hemoglobin, 67 g/L), hypoalbuminemia (serum

albumin, 20 g/L), and CRP of 89 mg/L. The patient underwent exploratory laparotomy and resection of the diseased ileocolonic segment with primary side-to-side anastomosis. The postoperative course was uneventful, and the patient was discharged in stable condition. The decision to initiate postoperative medical prophylaxis was postponed until endoscopic evaluation was performed.

At 6 months, the patient underwent ileocolonoscopy, which showed at least 10 aphthous ulcers in the neoterminal ileum with normal intervening mucosa consistent with i2b on the modified Rutgeerts score.<sup>1</sup> The patient was started on infliximab (5 mg/kg) and achieved clinical and endoscopic improvement of lesions on subsequent colonoscopy 6 months later. Despite reporting being free of symptoms, laboratory investigations 18 months after initiation of infliximab showed iron-deficiency anemia, and repeat colonoscopy demonstrated ulcerated, non-obstructive narrowing at the anastomosis and 12 ulcers in the neoterminal ileum. Infliximab concentrations were above the therapeutic range (8 mg/L); thus, he was switched to ustekinumab (Stelara, Janssen). The patient is currently well and in endoscopic and clinical remission 6 months following initiation of ustekinumab.

### Discussion

#### *Risk Stratification*

Despite declining surgical resection rates in CD,<sup>2,3</sup> surgery remains an important treatment modality in patients with penetrating complications, medically refractory disease, or, as in the described case, stricturing complications. In contemporary cohorts, the 5-year risk of surgical resection was estimated to be 18%, and the 5-year risk of a second resection was 17.7%.<sup>2</sup>

#### Corresponding author:

Dr Vipul Jairath, Division of Gastroenterology, Western University and London Health Sciences Centre, 339 Windermere Road, London, ON N6A 5A5, Canada; Tel: (519) 685-8500 ext 33655; Fax: (519) 663-3658; E-mail: [vjairath@uwo.ca](mailto:vjairath@uwo.ca)

The decision to institute postoperative medical prophylaxis is influenced by the presence of risk factors for postoperative recurrence: active smoking, prior intestinal resection, granulomas or myenteric plexitis in the resection specimen, penetrating disease, the presence of perianal disease, extensive ( $\geq 50$  cm) small bowel disease, and age 30 years or younger.<sup>4-6</sup> The majority of risk factors overlap among guidelines. However, there is some disagreement regarding the number of risk factors required for the institution of medical prophylaxis: the British Society of Gastroenterology mandates the presence of 2 risk factors,<sup>6</sup> the European Crohn's and Colitis Organisation requires the presence of 1 risk factor,<sup>4</sup> and the American Gastroenterological Association suggests individualized decision-making based on risk factors for recurrence without specifying the exact number of risk factors.<sup>5</sup> This divergence indicates that the risk factors have not been validated prospectively. Further, the extent to which these factors contribute to the risk of postoperative recurrence is uncertain, as illustrated by the PREVENT trial (as described in a following section).

The patient in the described case should ideally have received postoperative prophylaxis owing to the presence of penetrating complications and smoking. Moreover, supporting smoking cessation is an essential part of managing postoperative CD, as the risk of recurrence decreases to that of nonsmokers after cessation, which has been demonstrated in cohort studies.<sup>7,8</sup>

### Endoscopic Evaluation

Endoscopic evaluation is recommended between 6 and 12 months after ileocolic resection, regardless of whether medical prophylaxis was given. Endoscopic assessment guides subsequent decision-making about treatment institution or escalation. The strategy of treatment guided by endoscopic evaluation was compared with standard care without endoscopy in the randomized POCER trial.<sup>9</sup> In this trial, all patients received a 3-month course of metronidazole with the addition of azathioprine in high-risk patients or adalimumab in high-risk patients intolerant of thiopurines. Patients in the active arm underwent ileocolonoscopy at 6 months to guide further treatment, whereas patients in the standard arm continued their treatment. Patients from both arms underwent ileocolonoscopy at 18 months. It should be noted, however, that none of the medical interventions from the trial (azathioprine, adalimumab, metronidazole) are supported by randomized controlled trials, which makes the POCER trial difficult to interpret.

The endoscopy-driven strategy was superior to standard management for the primary endpoint of endoscopic recurrence at 18 months (49% [60/122] vs 67% [35/52];  $P=.03$ ). Patients in the active arm were also more likely

**Table.** Endoscopic Indices Used for the Assessment of Postoperative Crohn's Disease

Rutgeerts Score <sup>10</sup>	
i0	No lesions
i1	$\leq 5$ aphthous lesions in the neoterminal ileum
i2	$>5$ aphthous lesions with normal intervening mucosa or skip area of large lesions or lesions confined to the ileocolonic anastomosis
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Large ulcers with diffuse mucosal inflammation or nodules or stenosis in the neoterminal ileum
Modified Rutgeerts Score <sup>1</sup>	
i0	No lesions
i1	$\leq 5$ aphthous lesions in the neoterminal ileum
i2a	Lesions confined to the ileocolonic anastomosis (including anastomotic stenosis)
i2b	$>5$ aphthous ulcers or large lesions, with normal mucosa in between, in the neoterminal ileum (with or without anastomotic lesions)
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Large ulcers with diffuse mucosal inflammation or nodules or stenosis in the neoterminal ileum
REMIND Score <sup>12</sup>	
<i>Anastomotic lesions (&lt;1 cm in length after the anastomosis)</i>	
A(0)	No lesions
A(1)	Ulcerations covering $<50\%$ of the anastomosis circumference
A(2)	Ulcerations covering $>50\%$ of the anastomosis circumference
A(3)	Anastomotic stenosis
<i>Ileal lesions</i>	
I(0)	No lesions
I(1)	$\leq 5$ aphthous lesions in the neoterminal ileum
I(2)	$>5$ aphthous lesions with normal intervening mucosa or skip areas of larger lesions
I(3)	Diffuse aphthous ileitis with diffusely inflamed mucosa
I(4)	Diffuse inflammation with larger ulcers
POCER Index <sup>16</sup>	
0	No anastomotic ulcers
1	Superficial anastomotic ulcers ( $<2$ mm in depth), $<25\%$ circumferential extent
2	Superficial anastomotic ulcers ( $<2$ mm in depth), $\geq 25\%$ circumferential extent
3	Deep anastomotic ulcers ( $\geq 1$ ulcer with $\geq 2$ mm depth), $<25\%$ circumferential extent
4	Deep anastomotic ulcers ( $\geq 1$ ulcer with $\geq 2$ mm depth), $\geq 25\%$ circumferential extent

to have complete mucosal normality (ie, no lesions in the neoterminal ileum or at the ileocolonic anastomosis) at 18 months (22% [27/122] vs 8% [4/52];  $P=.03$ ).

Endoscopic assessment in the POCER trial was performed using the Rutgeerts score (Table).<sup>10</sup> This score was developed in 1990 to stratify patients for risk of clinical recurrence. The score is widely used in clinical practice and in clinical trials, although it has not been fully validated, with instrument responsiveness remaining unknown. The score has substantial inter-rater reliability among expert endoscopists, although there was some disagreement in defining aphthous ulcers in the neoterminal ileum, possibly owing to the difficulty of separating small ulcers from mucus or residual debris.<sup>11</sup> A Rutgeerts score of i2 is used as the threshold for recurrence to trigger treatment institution or escalation in patients already receiving treatment. This was also the threshold used in the POCER trial.

The i2 category of the Rutgeerts score is itself heterogeneous, encompassing lesions confined to the ileocolonic anastomosis and lesions in the neoterminal ileum. The hypothesis that anastomotic lesions have a better prognosis than lesions of the neoterminal ileum led to the development of the modified Rutgeerts score (Table), where i2a denotes lesions confined to the ileocolonic anastomosis and i2b encompasses all other lesions classified as i2 on the original score (>5 aphthous ulcers or large lesions, with normal mucosa between, in the neoterminal ileum, regardless of concomitant anastomotic lesions).<sup>1</sup>

The operating properties of the modified Rutgeerts score have not been prospectively evaluated, and there are no data on the consequences of using the modified, rather than the original, version to guide treatment choices. However, there are retrospective data on the risk of recurrence for i2a vs i2b lesions. When interpreting the findings of these studies, a distinction should be made between clinical recurrence and endoscopic progression (defined as the evolution from i2 to i3/i4 lesions). Symptom-based scores in postoperative CD are neither sensitive (only a minority of patients with endoscopic recurrence are symptomatic) nor specific (abdominal pain and diarrhea in the postoperative setting can have causes other than active CD).

In a French prospective multicenter cohort study of 225 patients (193 with long-term follow-up), a differential risk of clinical recurrence (symptoms of active CD with endoscopic or radiologic evidence of active disease) was observed between i2a and i2b in comparison with i0. Patients with i2b lesions had a significantly shorter recurrence-free survival than patients without lesions (i0); however, there was no difference in recurrence-free survival between patients with i2a and patients with i0.<sup>12</sup> In this cohort, anastomotic stenosis was the only

anastomotic lesion associated with subsequent recurrence or obstructive complications. Patients did not undergo routine endoscopy after the first assessment at 6 months, so asymptomatic endoscopic recurrence or progression beyond i2a may have been overlooked.

In a retrospective cohort study of 365 patients from 2 referral centers in France and Belgium, clinical recurrence-free survival (CD-related symptoms with CRP >5 mg/L) did not differ between patients with i2a or i2b at their first postoperative endoscopy.<sup>13</sup> No difference was observed for surgical recurrence, either.

In the 2 studies assessing the evolution of endoscopic lesions, the risk of progression to i3/i4 was higher for i2b lesions than with i0/i1 lesions.<sup>14,15</sup> The risk of progression for i2a lesions was no different than for i0/i1 lesions (Ollech and colleagues: hazard ratio, 2.30; 95% CI, 0.80-6.66<sup>14</sup>; Bachour and colleagues: adjusted odds ratio, 2.11; 95% CI, 0.89-4.97<sup>15</sup>). In a sensitivity analysis of one of the studies defining endoscopic progression as at least i2b (rather than i3/i4), the risk was indeed higher for i2a lesions than for i0/i1 lesions.<sup>15</sup>

Taken together, these data imply a gradient of increasing risk for recurrence from i0/i1, across i2a to i2b. However, there are insufficient data to assume that the risk for recurrence in patients with i2a lesions is negligible and no different than for patients with i0/i1; studies conducted to date have been underpowered to show a statistically significant increased risk of recurrence when comparing i2a with i0/i1. Thus, there is uncertainty regarding the consequences of escalating or initiating treatment at a threshold of i2b, compared with i2 as a whole on the original scale.

Two further endoscopic indices for postoperative CD were recently developed: the REMIND score<sup>12</sup> and the POCER index (Table).<sup>16</sup> The REMIND score separates anastomotic lesions (subscore A) from ileal lesions (subscore I), with anastomotic lesions graded by their circumferential extent and ileal lesions scored by the original Rutgeerts score. The POCER index focuses solely on the anastomosis, grading the depth and circumference of anastomotic ulcers. Both indices require validation in larger independent cohorts, and their utility in therapeutic decision-making remains to be ascertained. Finally, a recently published post-hoc analysis of the PREVENT trial indicated that a dedicated endoscopic index for postoperative CD may not even be necessary: the Simple Endoscopic Score for CD and its derivative, the Modified Multiplied Simple Endoscopic Score for CD, had similar predictive power compared with the Rutgeerts score, with the potential advantage of accounting for colonic recurrence as well.<sup>17</sup>

The patient in the described case had numerous aphthous ulcers in the neoterminal ileum, which is consistent

with i2 on the Rutgeerts score and i2b on its modified version. These findings are diagnostic of endoscopic recurrence, warranting initiation of treatment.

### **Medical Treatment**

None of the available biologics or small molecule drugs have received regulatory approval specifically for the prevention of postoperative CD recurrence. Postoperative CD is not specifically mentioned in regulatory guidelines, but a coprimary endpoint of symptomatic and endoscopic remission is mandated for the registration of new medicinal products for the treatment of CD.<sup>18</sup> As already outlined, symptom-based scores are unreliable in the postoperative setting; endoscopic recurrence is usually asymptomatic, and clinical symptoms do not necessarily reflect active CD.

These points are well illustrated by the findings of the PREVENT trial, which evaluated the efficacy of infliximab to prevent postoperative recurrence.<sup>19</sup> Patients with at least 1 risk factor for recurrence were randomized to receive infliximab (5 mg/kg every 8 weeks without the usual induction sequence) or placebo within 45 days of surgery. The primary endpoint was clinical recurrence, defined as a composite outcome consisting of a CD Activity Index score of more than 200 and an at least 70-point increase from baseline, and endoscopic recurrence (Rutgeerts score  $\geq$ 2, determined by a central reader) or development of a new or redraining fistula or abscess before or at week 76. Endoscopic recurrence was a secondary outcome. A smaller percentage of patients in the infliximab group had clinical recurrence compared with the placebo group, but the difference was not statistically significant (12.9% [19/147] vs 20% [30/150];  $P=.097$ ). The comparison for endoscopic recurrence clearly favored infliximab (22.4% [33/147] vs 51.3% [77/150];  $P<.001$ ). Only 18.1% (20/110) of patients with endoscopic recurrence also had recurrence based on the CD Activity Index, which underscores the shortcomings of symptom-based scores in the postoperative setting.

Further features of the PREVENT trial design may have contributed to the negative findings; infliximab was given without the usual 3-dose induction regimen, the use of concomitant immunosuppressants was optional, and 11.1% of patients had previously been exposed to infliximab. Taken together, these factors increased the risk of immunogenicity and subsequent failure of infliximab; antidrug antibodies were detected in 16.2% (all without immunosuppressants), but because a drug-sensitive assay was used, the true prevalence of immunogenicity was underestimated. Finally, the rate of recurrence was lower than expected based on prior studies of clinical risk factors, and the additive effect of multiple risk factors on the rate of recurrence was not replicated in the trial.

Endoscopic recurrence is a strong predictor of subsequent clinical recurrence. This association was explored in a systematic review of 37 studies with 4053 patients.<sup>20</sup> The risk of clinical recurrence in patients with endoscopic recurrence was 13-fold higher than in patients who did not experience endoscopic recurrence. The estimate was consistent regardless of study design (cohort study, randomized controlled trial) or patient subgroup (eg, prior exposure to biologics, longer disease duration). Overall, the rate of clinical recurrence without endoscopic recurrence was low, which may reflect the fact that the majority of studies also required objective markers to confirm that symptoms were the result of active CD. Taken together, these findings support the use of endoscopy as the primary endpoint in controlled trials of postoperative CD therapy.

A number of other drugs have also been tested in the setting of preventing postoperative recurrence, and the results of these trials are best summarized by a recent network meta-analysis.<sup>21</sup> Briefly, tumor necrosis factor (TNF)- $\alpha$  antagonists and thiopurines (both alone and in combination with nitroimidazole antibiotics) were superior to placebo in preventing endoscopic recurrence, whereas nitroimidazole antibiotics in monotherapy and 5-aminosalicylates were no more effective than placebo. TNF- $\alpha$  antagonists were more effective than thiopurines.

All guidelines offer the choice between thiopurines and TNF- $\alpha$  antagonists as the initial therapy choice, which is surprising, given the lower efficacy of thiopurines and the lack of a single compelling trial supporting their use.<sup>4,6</sup> In the randomized placebo-controlled TOPPIC trial of mercaptopurine, the drug was superior to placebo in preventing clinical recurrence in the subgroup analysis of smokers, but not the entire trial population.<sup>22</sup> These results were further corroborated by a recently published individual patient data meta-analysis of 6 studies comparing TNF- $\alpha$  antagonists with thiopurines in the postoperative setting.<sup>23</sup> TNF- $\alpha$  antagonists were superior to thiopurines for the prevention of endoscopic and clinical recurrence both in low- and high-risk patients.

On balance, given the superiority of TNF- $\alpha$  antagonists for preventing endoscopic recurrence and safety concerns with long-term use of thiopurines,<sup>24-26</sup> the former should be favored in the postoperative setting. There are only limited data on treatment choices for postoperative patients who have failed multiple biologics. A logical approach would be to choose a drug with an alternative mechanism of action in patients who had failed a TNF- $\alpha$  antagonist despite adequate drug concentrations.

Data on the effectiveness of biologics that are not TNF- $\alpha$  antagonists for the prevention of postoperative recurrence are gradually emerging from small uncontrolled series.<sup>27-30</sup> These findings are difficult to interpret, as patients treated with vedolizumab (Entyvio, Takeda)

or ustekinumab have almost invariably experienced failure of TNF- $\alpha$  antagonists. A randomized controlled trial of vedolizumab for the prevention of postoperative recurrence is ongoing (REPREVIO; EudraCT 2015-000555-24).

### Monitoring

Monitoring strategies beyond the first year are less well defined. The use of noninvasive modalities, such as fecal calprotectin and intestinal ultrasound, appears particularly attractive for this purpose, given their high negative predictive value, and endoscopic assessment would only be used after noninvasive methods suggested recurrence.<sup>31,32</sup>

The role of fecal calprotectin in the monitoring of postoperative CD was evaluated in the POCER trial.<sup>33</sup> Fecal calprotectin was measured before surgery and 6, 12, and 18 months after surgery. Concentrations greater than 100 mg/kg had a negative predictive value of 91% for endoscopic recurrence. Using a fecal calprotectin-based monitoring algorithm, 47% of patients could have avoided ileocolonoscopy. Fecal calprotectin was also useful in monitoring response in patients with endoscopic recurrence who stepped up treatment. An identical negative predictive value was also found in a small Japanese prospective study in which fecal calprotectin was used to monitor patients after their first ileocolonoscopy.<sup>34</sup>

A systematic review of 10 studies that included 536 patients found that the overall sensitivity, specificity, and diagnostic accuracy of intestinal ultrasound to diagnose postoperative recurrence was 94%, 84%, and 90%, respectively.<sup>31</sup> Noninvasive monitoring approaches of postoperative CD thus merit further evaluation in larger prospective studies.

### Conclusion

The therapeutic dilemmas illustrated with the described case highlight the paucity of high-quality studies in postoperative CD and the weaker evidence base compared with luminal CD. Decisions on prophylactic medical treatment are guided by risk stratification for disease recurrence. No drug is approved specifically for the prevention of postoperative CD; however, infliximab has the highest-quality data from a randomized placebo-controlled trial where it was superior in preventing endoscopic, but not clinical, recurrence. Data on biologics other than TNF- $\alpha$  antagonists in the postoperative setting are currently limited to uncontrolled series. Patients should undergo endoscopy between 6 and 12 months after surgery to guide decisions of treatment initiation or escalation after surgery. The Rutgeerts score has been most widely used to assess the endoscopic appearance after ileocolonic resection. Significantly more study is required to

define the optimal management of postoperative CD in terms of both treatment and monitoring.

### Disclosures

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