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Editorial: predicting recurrence of Crohn's disease after surgical resection—close to a crystal ball

Endoscopic recurrence of Crohn's disease is nearly universal within 5 years of surgery.[1-3] However, rates of early recurrence vary widely from 30%-90%. Hence, to avoid over-treatment and medication-related costs and adverse events, routine use of prophylactic therapy is not recommended.[4] However, waiting routinely for endoscopic recurrence before starting therapy is also not recommended since the efficacy of therapy may be lower in the presence of established severe endoscopic recurrence. A key knowledge gap identified in clinical guidelines from the American Gastroenterological Association[1,4] are factors that can accurately risk-stratify patients. This would identify those at high risk of recurrence who may benefit from early prophylactic therapy vs those at low risk of recurrence where endoscopy-guided therapy within 6-12 months after surgery may be reasonable.

Auzolle and colleagues have precisely addressed this gap.[5] In a meticulous prospective nationwide cohort study from the REMIND group, comprising nine academic centres in France, the investigators systematically analysed risk factors associated with endoscopic recurrence within 6-12 months of surgical resection for Crohn's disease. Based on 289 patients (47% with endoscopic recurrence), the investigators identified male sex, active smoking and prior intestinal resection as risk factors associated with recurrence. These findings were consistent in sensitivity analysis attesting to their robustness. While several of these factors have been previously identified as important risk factors, most studies were retrospective with inherent biases.[1-3,6] In addition, to further inform clinical decision-making, they analysed the impact of having zero, one or two or more of these risk factors on endoscopic recurrence. While only 29% of patients without any risk factor experienced endoscopic recurrence, 45% of patients with one risk factor experienced recurrence (odds ratio OR = 2.1, $P = 0.03$) and 74% of patients with two or more risk factors experienced endoscopic recurrence (OR = 6.9, $P < 0.001$). Although investigators did not develop or validate a clinical prediction tool, this knowledge directly informs and promotes shared decision-making between patients and physicians to assess the need for post-operative prophylactic therapy.

In addition, the investigators also identified that post-operative prophylaxis with tumour necrosis factor (TNF)-α antagonists was associated with 50% lower odds of endoscopic recurrence. This finding too was stable in a propensity score-matched analysis, attesting to the efficacy of prophylactic therapy as previously demonstrated.[1,6-8] Interestingly, they also observed that 8/10 TNF-α antagonist-treated patients with anti-drug antibodies at the time of surgery experienced endoscopic recurrence, compared to 13/43 (30%) without anti-drug antibodies. It is unclear whether those with anti-drug antibodies were treated with the same or different TNF-α antagonist (only 36% patients were treated with same TNF-α antagonist after surgery as before). So, while it is unclear whether endoscopic recurrence occurred in a subset of patients who had already developed immunogenicity to their TNF-α antagonist agent at the time of surgery, it highlights the potential importance of checking for anti-drug antibodies at the time of surgery, before starting prophylactic therapy with the same or a different TNF-α antagonist.

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LINKED CONTENT

This article is linked to Auzolle et al and Allez and Auzolle papers. To view these articles visit https://doi.org/10.1111/apt.14944 and https://doi.org/10.1111/apt.14998.

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Editorial: predicting recurrence of Crohn's disease after surgical resection—Close to a crystal ball. Authors' reply

On behalf of our colleagues from the REMIND study group, we thank Dr Siddharth Singh for his editorial.[1] Dr Singh highlights the importance of optimal risk stratification in the management of Crohn's disease (CD) patients after surgery. In our study, we used early endoscopic recurrence as the primary endpoint.[2] Ileocolonoscopy is recommended within the first year after surgery, since the severity of endoscopic recurrence predicts the clinical course in the following years.[3,4]

Dr Singh underlined the hypothesis that the efficacy of therapy could be lower in the presence of established severe endoscopic recurrence. Indeed, patients with severe early endoscopic recurrence may have received the treatment too late and would have benefited from initiation of optimal therapy within the weeks following surgery. In the POCER study, patients in the active care group who stepped up therapy for endoscopic recurrence (Rutgeerts score $\geq$ i2) at 6 months, mucosal healing at 18 months was achieved in less than 40% of patients.[5] For these patients, an immediate post-operative introduction of the treatment might have allowed a higher rate of mucosal healing. In the REMIND study, we are following our patients long term to analyse the correlation between early endoscopic recurrence and long-term outcome. We will assess whether the benefit of early introduction of anti-TNF therapy in patients at high risk is more efficient than initiation after endoscopic recurrence.

As pointed out in Dr Singh's editorial, we did not propose a clinical prediction tool. The risk factors identified in our study should be integrated in clinical practice to propose to the patient a personalised approach. However, the predictive value of clinical risk factors is still limited. This fully justifies the search for predictive and explanatory biomarkers that could benefit from an intervention perspective. Indeed, we strongly believe that prediction could be improved in the near future through a better classification of CD and a better understanding of post-operative recurrence. This is the reason why, on the same prospective cohort of CD patients followed from surgery to a post-operative endoscopy 6 months later, we have built an extensive bio-bank based on mucosal samples collected at time of surgery and endoscopy. We are performing gene transcription, microbiome and genetic analyses, to identify biomarkers that could be used as predictors of early post-operative endoscopic recurrence. Our objective is to move from a personalised approach to precision medicine, guided by biomarkers as a "crystal ball".

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