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Editorial

Prognostic Biosignatures at Ileocecal Resection: Hope or Reality?

In 1932, Burrill Bernard Crohn and colleagues described regional ileitis in their paper 'Regional ileitis: a pathologic and clinical entity', based on observations in the surgical theatre. Surgery was the primary treatment option for many years, and extensive resections were regarded as a potential cure. Since the description by Crohn *et al*., advances in our understanding of the pathogenesis of Crohn's disease have led to the development of an increasing number of treatment options. Today, surgery is often replaced by medical therapy.

Crohn's disease is a complex clinical entity, and the inflammation is often accompanied by various degrees of fibrosis. Already at diagnosis, approximately 20% of patients with Crohn's disease experience symptomatic strictures. Even though novel anti-inflammatory therapies can induce and maintain endoscopic remission, there are no drugs with a proven anti-fibrotic effect in Crohn's disease. In addition, Ponsioen *et al*. recently challenged the positioning of surgery in patients with limited non-stricturing, ileocaecal Crohn's disease by demonstrating the benefits of primary laparoscopic ileocecal resection vs anti-tumour necrosis factor [anti-TNF] therapy.[1]

However, ileocaecal resection rarely cures Crohn's disease. In the absence of treatment, the postoperative recurrence rate is between 65 and 90% within 12 months of the resection. Its severity may range from some aphthous ulcers to pronounced inflammation and narrowing, with a high likelihood of clinical symptoms and a need for re-resection.[2] Early introduction of biologics is the most effective strategy for preventing disease occurrence. However, routine use of these drugs may raise concerns about an increased risk of drug-related side effects, costs and insufficient long-term effects. Postoperative endoscopic recurrence precedes the onset of clinical symptoms, and assessment of its severity may, in part, predict future clinical relapse. In the absence of other prognostic biomarkers that could guide clinicians and individualize postoperative therapy, existing guidelines recommend ileocolonoscopy 6–12 months after surgery. Evidence from the Postoperative Crohn's Endoscopic Recurrence [POCER] trial demonstrates that risk-stratification based on clinical risk factors in combination with early colonoscopy and treatment step-up for recurrence is superior to conventional drug therapy alone for preventing postoperative recurrence.[3]

Nevertheless, proactive care requires continuous monitoring because early endoscopic remission does not preclude later disease recurrence. Repeated measurements with non-invasive markers, i.e. faecal [f]-calprotectin, can be used to guide the timing of endoscopy and better detect postoperative recurrence.[2,4] C-reactive protein [CRP] has been proposed as an alternative marker of postoperative recurrence, but its performance is inferior to that of f-calprotectin.[2,5] However, appropriate cut-offs for defining postoperative recurrence are debated, and endoscopic remission may not be associated with transmural healing. To assess transmural activity and potential fibrosis, additional modalities such as magnetic resonance imaging or intestinal ultrasound are needed. To advance the field, there is a need to identify reliable markers of future disease course, allowing differentiation of patients at high vs low risk of recurrence already at surgery. Recent work indicates a potential for microbiota to predict postoperative endoscopic recurrence. Sokol *et al*. examined ileal mucosa-associated microbiota by 16S gene sequencing of biopsies from 201 prospectively recruited French patients with Crohn's disease.[6] Gut microbiota at the time of ileocolonic resection was predictive of endoscopic recurrence within the cohort, but postoperative anti-TNF therapy also had a pronounced effect on recurrence rates. Even though the authors concluded that gut microbiota might be used to define patients at increased risk of postoperative relapse,[6] the dynamics of its temporal composition may challenge the use of gut microbiota-based signatures for decision-making in clinical practice.

There is a growing interest in examining serum and plasma protein profiles to identify potential predictive and prognostic biosignatures of inflammatory bowel disease.[7] Novel techniques, such as the proximity extension assay, allow screening of many proteins with high sensitivity and specificity. In this issue of the *Journal of Crohn's and Colitis*, Walshe and colleagues present their results of 92 examined inflammatory proteins in 213 Crohn's disease patients who underwent ileocolonic resection across six centres of the NIDDK Inflammatory Bowel Disease Genetics Consortium.[8] The median time from surgery to the first colonoscopy was 7 months, and serum proteins at baseline were profiled using the Olink Inflammation I panel. By using a multilevel Bayesian model and defining recurrence as a Rutgeerts score ≥i2, the authors identified a predictive signature of postoperative recurrence. The signature comprised CXCL9, MMP1, IL5, ST1A1 and log CRP, and based on comparisons of cross-validated area under the receiver operating characteristic curve estimates, the signature outperformed CRP alone.[8]

Furthermore, the authors also correlated protein levels with the Rutgeerts score while stratifying for the use of

postoperative anti-TNF treatment [yes/no]. Interestingly, reported proteins differed between the groups. In patients on postoperative anti-TNF therapy, higher Rutgeerts scores were associated with higher levels of several proteins, and among those CXCL9, CRP, MMP-1 and CXCL11 were the top upregulated proteins. Notably, of those top-markers, only MMP-1 correlated with the Rutgeerts score in Crohn's disease patients who were not treated with anti-TNF agents. Both CXCL9 and CXCL11 are CXCR3 receptor ligands. The association between CXCL9, CXCL1 and the Rutgeerts score was limited to anti-TNF-treated patients. As Walshe and colleagues point out in their discussion, this finding may indicate an important role for the CXCR3 axis in 'breakthrough' inflammation in the context of postoperative anti-TNF therapy.[8] However, these speculations are based on indirect comparisons of differentially regulated proteins after stratifying for anti-TNF therapy exposure. Direct comparisons of CXCL9 and CXCL11 levels in patients on anti-TNF therapy vs other treatments could have provided additional information. Nevertheless, the fact that a positive correlation between CXCL9 and CRP has consistently been reported[8,9] questions if the correlation between CXCL9 levels and Rutgeerts score in the NIDDK cohort is specific for anti-TNF treatment only. In contrast to CXCL9 and CXCL11, MMP-1 seemed to be a treatment-independent marker of recurrence and was here reported to be highly expressed in activated fibroblasts.[8] Bourgenje *et al*. recently also described a *cis* protein quantitative trait locus [pQTL] for MMP-1, emphasizing genetic implications for MMP-1 in IBD.[9]

In an abstract from the ECCO congress 2018, Machiels *et al*. present their preliminary results on a protein signature discriminating patients with and without post-operative endoscopic recurrence.[10] The design of Machiels *et al*.'s study was comparable to the current paper by Walshe and colleagues. Although both groups used the same selection of proteins, the inflammation panel by Olink, they found a different set of signature proteins. Indeed, only the sulfotransferase ST1A1 is a common protein of both signatures. However, different methodological aspects, including the statistical analyses, might explain those differences. Interestingly, Machiels and colleagues found additionally changes in the microbiota, which also discriminated recurrence from remission and added value to the protein model, based on area under the receiver operating characteristics curve analyses.[10]

Biomarker research is highly relevant for the implementation of personalized medicine in Crohn's disease. The paper by Walshe *et al*. focuses on the postoperative setting. Remarkably, the signature proteins correlating with the Rutgeerts score represented few 'new names' in the context of IBD. This finding indicates that the field would benefit from a more detailed understanding of the various proteins. For instance, are the CXCR3 receptor ligands markers of recurrence, refractoriness to anti-TNF treatment or general inflammation? Improved characterization of each protein's functional properties may translate into transferable interpretations and ultimately improve acceptance in clinical care. Importantly, independent validation cohorts should be used to prove the generalizability of identified markers. Also, a clinically useful test may need a higher sensitivity and specificity than available from the presented signature. An even more comprehensive analysis of accessible blood-based markers is a natural second step. Until those obstacles are overcome, the combination of repeated f-calprotectin measurements and endoscopic assessment probably remains the best preventative approach.

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Conflict of Interest

JH has consulted or served on advisory board for AbbVie, Celgene, Celltrion, Ferring, Galapagos, Gilead Sciences, Index Pharma, Janssen, Lincs, MSD, Novartis, Olink Proteomics, Pfizer, Prometheus Laboratories Inc., Sandoz, Shire, Takeda, Thermo Fisher Scientific, Tillotts Pharma and Vifor Pharma, and received grant support from Janssen, MSD and Takeda. DB reports personal fees from Ferring, Janssen and Takeda outside the current work. BS discloses no conflicts.

Author Contributions

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