



## Postoperative thiopurines in smokers with Crohn's disease



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Crohn's disease is a lifelong disease that is often not cured by resection of all macroscopic lesions and nearly always recurs clinically within a few years after so-called curative surgery. Thus, a maintenance treatment is needed in patients who undergo surgery. Thiopurines (azathioprine and mercaptopurine) are the cornerstone of maintenance treatment in Crohn's disease and decreased the risk of postoperative clinical recurrence compared with placebo in two randomised trials published at the beginning of this century.<sup>1</sup> However, the effect was modest; pooling the results from the two trials gave a risk ratio of 0.74 (95% CI 0.58–0.94).<sup>1</sup> Findings from other trials comparing thiopurines with mesalazine did not show significant differences.<sup>1</sup> Moreover, impressive results were reported from pilot studies, showing the great efficacy of anti-tumour-necrosis-factor (anti-TNF) drugs in this setting.<sup>2</sup> For these reasons, and because of problems of tolerance in up to 20% of patients, many physicians became reluctant to use thiopurines as preventive drugs, preferring to prescribe anti-TNF drugs in patients with a high risk of recurrence and to give mesalazine or no treatment at all in low-risk patients. Thus, the relevance of a new trial re-investigating the benefits of mercaptopurine after surgery could be questioned.

However, the TOPPIC trial<sup>3</sup> of mercaptopurine to prevent recurrence of Crohn's disease after surgical resection, published in *The Lancet Gastroenterology & Hepatology*, is unique because of its high methodological quality, in particular its long duration of up to 3 years, the masking of participants, the dosing of the drug, and the choice of a solid and pragmatic primary endpoint of well defined clinical recurrence and need for associated medical or surgical treatment. In the trial, 128 patients with Crohn's disease received mercaptopurine and 112 placebo. 16 (13%) patients in the mercaptopurine group versus 26 (23%) patients in the placebo group had a clinical recurrence of Crohn's disease and needed anti-inflammatory rescue treatment or primary surgical intervention (adjusted hazard ratio [HR] 0.54, 95% CI 0.27–1.06;  $p=0.07$ ; unadjusted HR 0.53, 95% CI 0.28–0.99;  $p=0.046$ ). This finding of reduced clinical recurrence with mercaptopurine is not new, but this result should be put in parallel with more recent data on anti-TNF drugs: the PREVENT study<sup>4</sup> did not show a significant effect of infliximab on prevention

of postoperative clinical recurrence by month 18, and, although not designed for this objective, the POCER study<sup>5</sup> showed that adalimumab had some efficacy, but this was not as universal as expected, with 43% of patients given adalimumab postoperatively experiencing endoscopic recurrence at 2 years. When considering long-term prescription of a drug, long-term tolerance and efficacy, constraints, and costs need to be taken into account; this would favour thiopurines over anti-TNF drugs in most patients.

The key finding of the TOPPIC trial was the particular efficacy of mercaptopurine in smokers. 55 (23%) patients included in the study were active smokers. In this subgroup, mercaptopurine was effective at preventing postoperative recurrence (HR 0.13, 95% CI 0.04–0.46), with a number needed to treat to prevent one recurrence of only three. Conversely, the effect of mercaptopurine was not significant in non-smokers. Although unexplained, the efficacy of thiopurines in smokers has been known for around 20 years.<sup>6</sup> Smokers have a more severe disease than do non-smokers, and they need more immunosuppressants and surgery; active smoking is recognised as the most important predictive factor of disease recurrence. Because smokers have a high risk of early postoperative recurrence, surgery must be avoided or postponed as long as possible and all efforts are needed to achieve smoking cessation before surgery. That said, results of smoking cessation programmes are disappointing in this population. When a smoker needs surgery, findings from the TOPPIC trial<sup>3</sup> suggest that thiopurines should be started or re-started within the 3 months after surgery, with a high probability of delaying postoperative recurrence.

Postoperative recurrence, with the sequence of histological lesions, endoscopic ulcerations, clinical symptoms, then re-operation, is an amazing model to understand the natural history of Crohn's disease and to test treatments. The place of thiopurines in the management of Crohn's disease has been debated during recent years, particularly after the two negative trials testing the efficacy of azathioprine in very early Crohn's disease<sup>7,8</sup> and the evidence of an increased, albeit small, risk of malignancy.<sup>9</sup> In fact, the conclusion of the RAPID trial<sup>7</sup> was not that azathioprine was useless, but that there was no need to start azathioprine very early in the

disease course. Thiopurines are efficacious in 40–50% of patients with Crohn's disease. They are safe before age 65 years and in people who test positive for Epstein-Barr virus, and are safe and particularly efficacious in smokers. They should remain a major maintenance treatment for Crohn's disease, provided that their dosing is sufficient or optimised.<sup>10</sup> In this regard, it is noteworthy that the hazard of clinical recurrence decreased when the concentration of thioguanine nucleotides, a marker of compliance and adequate dosing, increased in the TOPPIC trial.

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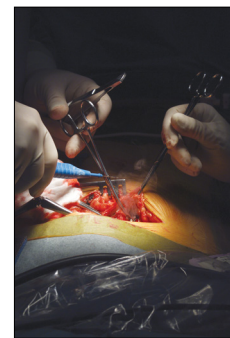
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## A new technique to improve surgery for peritoneal colorectal metastases?

I congratulate Niels Harlaar and colleagues for their Article<sup>1</sup> on molecular fluorescence-guided surgery for peritoneal carcinomatosis of colorectal origin. It is an exciting study with concrete implications for peritoneal surface surgeons. In other locoregional metastatic colorectal cancer sites, such as the liver and lungs, the most important factor to prevent a new recurrence and ultimately prolong survival is an R0 resection. In liver surgery, intraoperative ultrasound augmentation of the surgeon's visual and palpation skills is common to improve identification of tumour nodules in the liver.<sup>2</sup> Preoperative CT staging and intraoperative ultrasound provide the surgeon with the detailed information needed to achieve precise surgical results during resections of colorectal liver metastases. This precision is very much absent in peritoneal surface surgery. No good preoperative radiological planning algorithms for peritoneal metastases exist and no intraoperative augmentations are available in clinical routine. Treatment decisions during surgery are often made intraoperatively according to the surgeon's own experience,<sup>3</sup> making

accurate surgical precision planning difficult. The present study<sup>1</sup> is a welcome initiative to alleviate this problem. The issue is shown in the completeness of cytoreduction score, for which a score of 0 is really equivalent to an R1 resection, in which microscopic residual tumours are assumed to remain. As such, hyperthermic intraperitoneal chemotherapy (HIPEC) is needed to eradicate the microscopic disease. However, as HIPEC has become widely adopted as standard treatment in Sweden instead of systemic chemotherapy for colorectal cancer with peritoneal metastases, we have noticed that patients are getting referred earlier at our centre. Instead of receiving one or two lines of chemotherapy before referral, the patients are referred for surgery when peritoneal disease is discovered leading to lower peritoneal cancer index scores. The ability to accurately identify the exact number of peritoneal metastases by visual enhancement, such as with a fluorescent dye attached to bevacizumab, could substantially enhance the surgical precision of peritoneal surface surgeons by ensuring a good margin to each lesion—perhaps even achieving R0 resections.



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