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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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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.14978.

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Editorial: which inflammatory bowel disease patients should be screened for Epstein-Barr virus infection?

Thiopurines remain an integral component of the armamentarium for inflammatory bowel disease (IBD), particularly in combination with biologic therapy. However, azathioprine and mercaptopurine are also associated with infection, marrow suppression, pancreatitis, and a four- to five-fold increased risk of lymphoproliferative malignancies.[1,2]

Several studies have reported an association between thiopurine-associated lymphoproliferative disorders and prior Epstein-Barr virus (EBV) infection. However, the absolute risk of lymphomas with thiopurines remains low, and has been estimated to be 0.9 per 1000 person-years.[1] More recently, Hyams and colleagues noted an association between thiopurines, incident EBV infection, and haemophagocytic lymphohistiocytosis (HLH).[3] The risk of HLH was lower than lymphoma, at 0.2 per 1000 person-years.[3,4] This association has prompted some to recommend universal EBV screening and thiopurine avoidance in seronegative individuals.[5]

Understanding the epidemiology of EBV infection in IBD is vital to formalising an EBV screening strategy. In the general population, EBV prevalence approaches 100% by the mid to late 20s.[6] However, there are limited data regarding EBV prevalence in IBD. In a Canadian cohort, the prevalence of EBV seropositivity was similar to that of the general population, approaching 100% by age 25.[6] Based on these data, a universal screening strategy to reduce the risk of EBV-driven HLH would not be cost-effective for those over 25 years. However, less is known about the incidence of primary infection.

de Francisco et al have added to the growing literature on EBV incidence and prevalence in IBD.[7] In an adult cohort of 1483 patients with IBD at a tertiary hospital, EBV prevalence was similar to that of the general population by age 25, at 97.4%. They then took an important additional step, prospectively following 37 patients who were seronegative. Eleven (29.7%) patients seroconverted over 4 years.[7] The risk of seroconversion was independent of age or gender; however, there was one case of HLH reported among this small cohort. This is one of the largest studies to date assessing the prevalence and incidence of EBV in patients with IBD.

Studies such as de Francisco's are crucial for identifying the most cost-effective age groups for EBV screening. While EBV antibody testing is inexpensive, the results have the potential to impact quality of life. Multiple studies have demonstrated that combination therapy is the most effective for inducing remission in IBD.[8,9] While serologic testing and thiopurine avoidance may minimise the risk of rare events such as HLH, this strategy will also negatively impact patients' quality of life, reduce response rates, and increase steroid exposures due to a reluctance to use combination therapy. A recent modelling study demonstrated that screening was not cost-effective for those over age 23, primarily due to this effect.[10] A better understanding of the age-specific prevalence and incidence of EBV infection in young adults will allow for more accurate modelling of these scenarios. These analyses will be imperative for reducing the risks of rare but serious complications such as HLH while also maximising the benefit of our most effective therapies for IBD.