treatments. In this study, the primary end-point was a reduction in lactulose-to-mannitol (LAMA) ratio compared with controls. LAMA is a surrogate marker of intestinal permeability, and therefore effectiveness of treatment.[1] The data presented shows no significant difference between treatment and control arms.

This was also the case in the only other previously reported larazotide acetate study.[3] Do we therefore use a reduction in symptoms as a measure of effectiveness, as has been demonstrated in the larazotide acetate 1 mg cohort? Although anti-tissue transglutaminase (tTG) antibodies were demonstrated to be lower in the treatment arms, compared with controls, there was still an increase compared with baseline, suggesting some gluten reaction even if symptoms were reduced. This raises the question of long-term safety, and the risk of coeliac disease-related complications. Histological assessment of treatment success may also be difficult with intraepithelial lymphocytosis still present in 40% of patients, despite adherence to GFD.[4]

Kelly *et al.* have chosen a group of patients in whom there was apparent good control of their coeliac disease with negative anti-tTG antibodies.[1] Is it justifiable to offer a treatment to patients whose disease is controlled with a simple nontoxic dietary measure? Would it be more appropriate to use this drug in patients who find it difficult to adhere to a GFD? Would patients who are unable to adhere to a GFD find it any easier to take regular medications? Previous suggestions for a 'gluten holiday' may suit medications of this nature more easily.[5] However, the average diet contains 13 g of gluten per day,[6] whereas the gluten challenge in this study was only 2.7 g, equivalent to 1 slice of bread per day. This may not satisfy a patient's desire to eat a normal diet.

Nevertheless, patients do not find GFD a satisfactory treatment and are open to the possibility of novel therapies.[5] The investigators should be commended for pursuing this novel option and demonstrating that larazotide acetate is a well-tolerated potential treatment, with good short-term safety. Perhaps the next step is targeting patients who are not adherent to a GFD and assessing the effect of larazotide acetate in this cohort.

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Commentary: larazotide acetate - an exciting new development for coeliac patients? Authors' reply

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We agree with Drs Mooney and Sanders that larazotide acetate may prove to be an exciting development for

clinicians and for patients with coeliac disease.[1, 2] As they indicate, this study highlights the importance of developing validated outcome measures for clinical trials in coeliac disease. Three groups of measures are coming to the fore: (i) patient-reported outcome tools designed and developed specifically to quantify symptoms that reflect coeliac disease activity; (ii) biomarkers of coeliac disease activity such as anti-tissue transglutaminase or anti-deamidated gliadin peptide antibodies; and (iii) quantitative or semi-quantitative histological measures such as villous height to crypt depth ratio or intraepithelial lymphocyte counts. Quantitative histology may allow for valid before and after comparisons even in study subjects with incomplete healing.

Although the ultimate goal in developing novel agents for coeliac disease may be to allow patients to safely resume a normal diet, this is not likely to be the first step. It is not expected that larazotide acetate will replace the gluten-free diet (GFD) as a primary and sole management for coeliac disease. Instead, it is envisaged as an adjunct to protect against exposure to hidden or contaminating gluten in those with coeliac disease. We agree that it may be especially valuable for those who, for whatever reasons, are unable to consistently maintain a GFD and for those whose disease remains active despite their best attempts to avoid gluten exposures; such a trial with larazotide acetate is now underway.

We find, in our discussions with patients, that many who would not be comfortable abandoning a GFD would nonetheless greatly welcome a medication that can provide them with symptom relief and protection against the effects of inadvertent gluten ingestion, thereby providing a substantial improvement in their health and quality of life on the GFD.

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Commentary: predicting relapse in Crohn's disease patients in remission with biologics

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This is an interesting study[1] made possible by funding rules in Hungary, whereby patients who enter remission after induction therapy with a biologic are obliged to cease therapy after 12 months maintenance. Whilst many clinicians regard these sorts of regulations (which exist in various forms around the world) as an impost on clinical decision-making – we must accept that funding constraints are real, and not likely to disappear, making cost effective medical practice a priority. Molnar *et al.* are to be congratulated for turning this impost into an opportunity from which we can all learn.

According to the authors, subjects were assessed at 12 weeks, following induction therapy with anti-TNF and responders (70% of those receiving induction) were offered 1 year of maintenance. So this is a selected group we are observing – who were all responders to induction.

Within 1 year of discontinuing biologic therapy, 66 recommenced, of these, 30 again responded, 6 went to surgery, and presumably 19 had ongoing active disease. This group is a concern, and an important message from this study is that there is a significant group for whom cessation of therapy has a significant risk. Of those not retreated within 1 year (55), 24 recommenced a biologic within 18–24 months. Thus, we are left with only 31 of the original cohort of 121 induction responders (26%) who are off therapy (and presumably well) after 24 months of cessation. This is a useful group to find, as savings made here may enable longer use of these effective therapies in those who need ongoing treatment.

In terms of predictors of successful cessation, the main message appears to be that 'winners' can be picked early (at 12 weeks) as those who were able to be off