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Letter: faecal volatile organic metabolites, promising biomarkers in inflammatory bowel disease and
Letter: faecal volatile organic metabolites as novel diagnostic biomarkers in inflammatory bowel disease. Authors’ reply

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Sir, We read with great interest the very valuable comments by both Furnari et al.,1 and Srinavas,2 regarding our recently published paper on faecal volatile metabolite in inflammatory bowel disease.3 In this study, we investigated the changes in faecal metabolites in different subsets of patients with Crohn’s disease and ulcerative colitis in comparison with healthy controls.

We agree with the comments by Furnari et al. about the lack of detailed dietary data about the study participants, which could have some potential effect on the changes observed in the faecal metabolites. This is a very important question and we had already highlighted this weakness of our study in the discussion section. Dietary variations can potentially affect the faecal metabolites through their effects predominantly on gut microbial dysbiosis.4,5 Patients with inflammatory bowel disease change their diet often in response to their symptoms, which makes it difficult (although not impossible) to collect very accurate dietary data. Such dietary comparison would have been easier and valuable in a precisely controlled setting – for example, in patients on elemental diet. None of the participants in this study is on elemental diet and due to the lack of detailed dietary data; the study was unable to shed any light on the effects of diet on the faecal metabolites. However, considering the high importance of diet, we are planning future studies to investigate any effect of diet on the faecal metabolites in IBD.

We are in agreement by the commentary offered by Srinavas regarding the influence of medication on the faecal metabolites. Detailed information about the medicines that the study participants were on was provided and the patients were continued on their existing medications. Our study did not detect any active or inactive metabolites of these medicines in the faeces of study participants. Although no solid conclusion could be drawn about the effect of medications on faecal metabolites with the current data but such an important question should be considered in future studies by including patients before and after starting drug treatment.

Our study detected a number of faecal metabolites such as heptanal, 1-octen-3-ol, 2-piperidinone and 6-methyl-2-heptanone, methanethiol, 3-methylphenol, short-chain fatty acids and ester derivatives that could be discriminatory in separating different groups of IBD. As pointed out by Srinavas et al., it would be ideal to find a single diagnostic metabolite in IBD which could provide information about the activity, type and extent of disease; however, the discrimination between the subtype of our study groups was shown by using a discriminatory model based on a number of metabolites. We discussed the important of each class (aldehyde, alcohol and ketones) of these discriminatory metabolites and its possible correlation with the gut microbial dysbiosis. With
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the development of more sophisticated analytical techniques, future research may be able to discover single diagnostic biomarker in IBD.

Our study groups comprised of patients with different extent, type and activity of the disease but we did not have any data regarding severity and duration of the disease. We believe this would be the next step in future studies to investigate the changes in faecal metabolites of patient at the initial diagnosis prior to commencing any medication, and in patients with different duration and severity of the disease.

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Letter: which patient profile for tacrolimus in ulcerative colitis?

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Sirs, We read with interest the article from Yamamoto et al. comparing oral tacrolimus with infliximab in their retrospective cohort of patients with glucocorticosteroid-refractory ulcerative colitis (UC).1 Their experience confirms two positive placebo-controlled trials and retrospective series showing that tacrolimus could be an alternative in this situation, as recommended by ECCO guidelines.2–5 Like ciclosporin, tacrolimus is a calcineurin inhibitor with good efficacy and safety profiles in UC. Moreover, and similar to ciclosporin, Yamamoto et al. have given tacrolimus as a 12-week bridging therapy to azathioprine, and then discontinued the drug.

Patient selection is crucial point for determining if oral tacrolimus should be used instead of ciclosporin in UC. Two different subsets of patient with glucocorticosteroid-refractory disease may receive ciclosporin: those admitted with an acute severe attack, not responding after a few days of intravenous glucocorticosteroids and requiring parenteral second-line medical therapy as an alternative to salvage colectomy; and, those with a non-acute severe flare who could be treated orally and managed as an out-patient. In the first situation, Truelove and Witts criteria are still recommended for identifying patients with a severe attack of UC, and the Lichtiger index is a valuable tool for assessing those refractory to intravenous glucocorticosteroids.5, 6

Unfortunately, Yamamoto et al. pooled those with an acute severe attack and a moderate exacerbation in their cohort, using the UC disease activity index (UC-DAI) as an inclusion criterion. The UC-DAI was developed 30 years ago in a study exploring salicylates enema in distal UC7 and has been used as a selection and judgment criteria in controlled trials evaluating tacrolimus in refractory UC.4 However, and as stated above, it is definitely not appropriate in this population. Moreover, as Yamamoto et al. did not provide the rate of patients with intravenous glucocorticosteroid failure at inclusion, the proportion of patients with acute severe UC in their cohort remains impossible to assess. Therefore, the best patient profile for oral tacrolimus in UC remains unclear.

Pending studies confirming tacrolimus efficacy in patients with acute severe UC, defined according to more usual criteria, physicians have only two validated medical options after glucocorticosteroid failure, which are ciclosporin and infliximab. Importantly, none of the others biologics available in UC, such as subcutaneous anti-tumour necrosis factor or anti-integrin monoclonal antibodies, have been evaluated in this special setting corresponding to an exclusion criteria from pivotal phase III studies.