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Letter: predicting azathioprine-associated pancreatitis in IBD—phenotype or genotype? Authors' reply

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EDITORS,

We thank Teich et al for their comments[1] and recognise there are differences in opinion with regards to the treatment algorithm as outlined in our study.[2] There are undoubtedly other risk factors associated with the onset of azathioprine (AZA)-induced pancreatitis, even beyond those identified by Teich et al in their own work.[3,4] Our algorithm was based on new insights regarding genetic determinants of variation in drug response as a way to guide clinicians on how to incorporate a novel genomic marker in clinical practice to enhance the safe use of AZA.

In terms of cost-effectiveness, we note that genotype-guided dosing of AZA using *TPMT* genotypes has been shown to be more cost-effective than standard practice in several studies.[5-7] Thompson et al (2014) published an economic evaluation of the TARGET Study (2011).[6,8] This group showed that *TPMT* genotyping resulted in lower costs compared to the standard practice of step-wise dose escalation with monitoring of biochemical and haematological parameters.[7] This confirmed work by Payne et al (2009) in an analysis of 6 retrospective economic evaluations of *TPMT*-guided AZA dosing, all of which emphasised its cost-effectiveness compared to standard practice.[6]

While the allele frequency of the rs2647087 variant genotype *is* relatively high, it *is* debatable whether or not AZA should be withheld from this population. The genomic data allow physicians to enter into a more informed discussion with their patient regarding the risks associated with AZA, whether used as monotherapy or in combination with a biologic, as well as discussion on other steroid-sparing alternatives such as methotrexate. In our cohort of patients, AZA-induced pancreatitis resulted in hospitalisation for all patients. Thus, while not severe, affected patients were of sufficient concern to warrant hospitalisation.

Lastly, Teich et al suggest that genomic-based dosing strategies for AZA are not effective, citing Coenen et al (2015).[9] The utility of pre-emptive *TPMT* genotyping is widely accepted. Canadian, American and British Gastroenterology Society guidelines, all advocate for pre-emptive *TPMT* genotyping prior to the introduction of thiopurine-based therapies in IBD.[10-13] The evidence for *TPMT*-guided dosing comes from robust mechanistic studies in addition to retrospective analyses supporting dose reduction in *TPMT* variant carriers summarised in the Clinical Pharmacogenetics Implementation Consortium Guideline.[14] Randomised control studies such as the Coenen et al (2015) study are insufficiently powered to show the benefit of *TPMT*-guided AZA dosing in general populations due to the rarity of variant *TPMT* genotypes. The greatest benefit is seen at the level of the variant carriers as was demonstrated by Coenen et al (2015).[9] A 10-fold reduction in haematologic adverse drug reactions was seen in the variant *TPMT* carriers in the intervention group (2.9%) versus the control group (22.9%) with a number needed to treat of five for patients carrying a *TPMT* risk allele.[9]

Ultimately, genotype-guided dosing algorithms for AZA have a role in IBD management particularly given the number of alternative therapeutic agents available, as well as the continued reduction in cost of genotype testing to enhance efficacy and reduce harm from AZA therapy.

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LINKED CONTENT

This article is linked to Wilson et al and Teich et al papers. To view these articles visit https://doi.org/10.1111/apt.14483 and https://doi.org/10.1111/apt.14545.

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Letter: extensive intestinal metaplasia is associated with the presence of incomplete intestinal metaplasia subtype and could be an easier marker for high risk of gastric cancer

EDITORS,

We read with great interest the elegant study published by Pittayanon et al[1] on the risk of gastric cancer (GC) in patients with gastric intestinal metaplasia (GIM). While we agree that incomplete GIM is an important risk factor for the development of GC, we think that the following issues should be considered.

First, extensive GIM has been recommended as a high-risk marker for GC.[2] This phenotype is also described as multifocal GIM.[2-4] Some previous studies have shown that multifocal GIM was significantly associated with the presence of the incomplete GIM subtype.[3,5] However, the number of biopsy specimens affected with GIM from each patient in this study was not addressed. Although the authors have included OLGIM stage in the multivariable analysis, it may not help to recognise the difference in rates of multifocal GIM between subgroups of patients with complete and incomplete GIM. We think that this variable should be included in the analysis to demonstrate that incomplete GIM is truly an independent risk factor for GC. This issue is clinically important as identifying multifocal GIM is more feasible than GIM subtyping, especially in the era of image-enhanced endoscopy.

Second, five out of 10 patients with incomplete GIM in this study progressed to high-grade dysplasia or GC. Furthermore, three patients progressed within 1 year of follow-up, which is much faster than the progression of GIM and almost similar to the progression of dysplasia to GC reported in recent studies.[4,6,7] Were these neoplasms detected at the same gastric locations where baseline incomplete GIM had been identified or from other locations? Our previous study in Vietnamese patients with non-ulcer dyspepsia showed that multifocal GIM, incomplete GIM and dysplasia tended to cluster in the same group of patients, and dysplastic lesions might not be endoscopically visible.[5] Is it possible that these patients already had