We believe that a limitation of the study is the use of red cell TGN to select suitable candidates for treatment. If we were to extrapolate the data presented, access to metabolite monitoring limits access to low-dose thiopurine allopurinol co-therapy to a subset of those who meet specific “metabolic” profiling (15% of nonresponders). We suggest that the use of combination therapy is not restricted in this way and refer to our published safety and response data\textsuperscript{3,4} to support this. These larger and longer term data sets report a similar safety and response rate achieved by removing complexity and increasing eligibility without compromising on outcomes.

The authors do highlight that the metabolic profiling using a commercially available assay has “modest sensitivity and specificity to predict adverse events” while it can “potentially (be) erroneous to rely solely on metabolite testing to guide therapy” questioning the clinical validity of this approach.\textsuperscript{5}

As the limitations of current monoclonal therapies become apparent, it is humbling to note that azathioprine continues to hold a place in modern therapeutic pathways. Based on this clinical trial and previously published experience, we believe that the low-dose thiopurine allopurinol combination holds a bigger promise for patients and healthcare systems.

We suggest that it is now timely to perform a randomised clinical trial to assess the safety and efficacy of first-line vs metabolite-directed low-dose thiopurine allopurinol co-therapy, and also to compare this co-therapy vs anti-TNF therapy in IBD.

With the promise of better, faster action and in tablet form, perhaps, it will prove a tough opponent to beat!

ACKNOWLEDGEMENTS

Declaration of personal and funding interests: None.

REFERENCES


DOI: 10.1111/apt.14798

Editorial: an argument for low-dose thiopurine allopurinol combination use as first-line therapy in inflammatory bowel disease—authors’ reply

We thank Drs. Ansari and Aziz for their insightful comments regarding the AAA study.\textsuperscript{1,2} We agree that the optimisation of small molecule therapy, by combining allopurinol with low doses of thiopurines, is a practical and cost-effective alternative to escalation of therapy with the expensive biologic agents. We also agree that utilisation of allopurinol to overcome thiopurine-related adverse events can occur without the need for monitoring of thiopurine metabolites as this has been demonstrated in a number of retrospective studies.\textsuperscript{3,4}

However, we do believe that if thiopurine metabolite testing is available, it should be used to maximise clinical efficacy. This is supported by a meta-analysis of more than 2000 patients which found that the odds ratio for clinical remission was 3.15 (95% confidence interval, 2.41-4.11) if 6TGN levels were above 260 pmol/8 \times 10^8 RBCs.\textsuperscript{5} Subsequently, the American Gastroenterological Association has recommended the use of thiopurine metabolite monitoring.\textsuperscript{6}

We hope that clinicians can now consider this combination as standard of care to overcome hepatotoxicity and other adverse
events, given both prospective and retrospective studies have demonstrated the efficacy of this manoeuvre. We believe this study further validates the use of thiopurine metabolite monitoring to help clinicians maximise efficacy of these small molecules. To further explore the role of allopurinol in thiopurine optimisation, a multicentre, randomised controlled trial comparing thiopurine monotherapy to allopurinol-thiopurine combination therapy de novo in thiopurine naive patients is currently underway in Australia.7

ACKNOWLEDGEMENT

The authors’ declarations of personal and financial interests are unchanged from those in the original article.2

ORCID

A. B. Friedman http://orcid.org/0000-0002-8106-1280
M. P. Sparrow http://orcid.org/0000-0003-2527-8044

LINKED CONTENT

This article is linked to Friedman et al and Ansari and Aziz papers. To view these articles visit https://doi.org/10.1111/apt.14571 and https://doi.org/10.1111/apt.14687.

A. B. Friedman M. P. Sparrow

REFERENCES

7. De novo combination allopurinol-thiopurine vs standard thiopurine in inflammatory bowel disease (IBD) patients escalating to immunomodulators: a randomized controlled trial (DECIDER Study). Australian New Zealand Clinical Trials Registry. ACTRN12613001347752

DOI: 10.1111/apt.14679

Editorial: transplantation in the setting of acute-on-chronic liver failure—calculating chances

“Necessity is the mother of taking chances,” Mark Twain once said. This is especially true in liver transplantation (LT), where the necessity for saving lives requires taking chances proceeding with transplant in less-than-optimised patients. Acute on chronic liver failure (ACLF) connotes acute, often critical, illness characterised by one or more organ failure in cirrhotic patients. It is associated with >90% mortality without transplant in the setting of multi-organ failure.1,2 The decision to transplant patients with current or recent ACLF was previously based solely on clinical judgement; however, data have recently shed a dim light on the post-transplant outcomes in this patient population.2-5

In a recent issue of Alimentary Pharmacology and Therapeutics, Huebener and colleagues evaluated the post-transplant outcomes in 250 patients with cirrhosis out of whom 98 had ACLF.6 Several important aspects of this study bear reviewing. A more granular breakdown on survival after transplant suggests only early post-transplant survival is impacted by ACLF. If a patient survives that first 90 days, then outcomes mirror those of other transplant recipients, which stands to reason. Most importantly, this study shows not all ACLF situations portend a poor outcome and that the patient that clinically improves prior to transplant is much more likely to survive that first 90 days. The authors propose an intriguing prognostication score essentially using the recovery of one organ system before transplant to better identify the ACLF patient more likely to survive.

Survival post-liver transplant in ACLF patients has been demonstrated in recent studies to range from 51% at 28 days5 to 89.4% at 90 days, likely reflecting differences in the severity of ACLF in the cohort analysed. Patients with ACLF 3 (≥3 organ failures) have been reported to have worse survival compared with stage 1 or 2 ACLF.5,7

Department of Gastroenterology, The Alfred Hospital, Melbourne, Vic., Australia
Email: a.friedman@alfred.org.au