

# UNIVERSITY OF BIRMINGHAM

## Research at Birmingham

### Reply

Hübener, Sina; Lohse, Ansgar W; Schramm, Christoph; Than, Nwe Ni; Oo, Ye Htun

DOI:

[10.1016/j.cgh.2016.03.013](https://doi.org/10.1016/j.cgh.2016.03.013)

License:

Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

*Document Version*

Peer reviewed version

*Citation for published version (Harvard):*

Hübener, S, Lohse, AW, Schramm, C, Than, NN & Oo, YH 2016, 'Reply', *Clinical Gastroenterology and Hepatology*. <https://doi.org/10.1016/j.cgh.2016.03.013>

[Link to publication on Research at Birmingham portal](#)

#### General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

#### Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.

Sina Hübener,\* Ye Htun Oo,‡ Nwe Ni Than, Christoph Schramm\*

\*Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; and ‡Centre for Liver Research, University of Birmingham Liver Unit, Birmingham, United Kingdom

**Reply.** We thank Meijer et al for their thoughtful commentary on our paper suggesting 6-Mercaptopurine (6-MP) as a second-line treatment option for patients with autoimmune hepatitis (AIH) and azathioprine (AZA) intolerance<sup>1</sup>.

We agree that in AIH patients with an insufficient response to AZA, as well as in patients with hepatotoxicity under higher doses of AZA, drug monitoring via measurement of 6-thioguanine nucleotides (6-TGN) and 6-methylmercaptopurine (6-MMP) could be useful. As Meijer et al pointed out, only a single study performed by Dhaliwal et al<sup>2</sup> suggested an association between 6-TGN concentrations above 220 pmol/ $8 \times 10^8$  red blood cells and remission in AIH, and the overlap between patients with and without remission was significant. More studies are needed to validate this cut-off for 6-TGN in AIH and to define concentrations of 6-MMP which would predict intolerance to treatment with AZA or 6-MP in patients with AIH.

Recent case series on the effect of allopurinol as addition to reduced doses of AZA or 6-MP in patients with an unfavorable metabolite ratio (“thiopurine shunter”) show promising results<sup>3-5</sup>, but larger studies are lacking. Usually, allopurinol is tolerated well, but this combination therapy includes a second drug with rare but potentially severe side effects, such as cytopenia or nephrotoxicity<sup>6</sup>.

There are several options for patients with AZA intolerance due to gastrointestinal symptoms, including low dose steroid monotherapy in patients with low disease activity. Splitting AZA dose may be successful in mild gastrointestinal side effects. However, patients quite often develop nausea, vomiting or diarrhea already at very low doses of 50mg or 75mg AZA per day. In these patients, we suggest 6-MP as a second-line treatment with good results. We would like to point out that 6-MP should not be considered as a class switch of immunosuppressive drugs in previously AZA-treated AIH patients. 6-MP could be a treatment option for Azathioprine intolerant young women who intend to have a family as MMF is contraindicated in this setting. Clearly, more research is needed to optimize the treatment of AIH with AZA, a drug with long term experience, well known side effect profile and, last but not least, low cost compared to second or third line treatment options.

1. Hübener S, Oo YH, Than NN, et al. Efficacy of 6-Mercaptopurine as Second-Line Treatment for Patients With Autoimmune Hepatitis and Azathioprine Intolerance. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2016;14(3):445-53.
2. Dhaliwal HK, Anderson R, Thornhill EL, et al. Clinical significance of azathioprine metabolites for the maintenance of remission in autoimmune hepatitis. *Hepatology.* 2012;56(4):1401-8.
3. Gardiner SJ, Garry RB, Burt MJ, et al. Allopurinol might improve response to azathioprine and 6-mercaptopurine by correcting an unfavorable metabolite ratio. *J Gastroenterol Hepatol.* 2011;26(1):49-54.
4. Al-Shamma S, Eross B, McLaughlin S. Use of a xanthine oxidase inhibitor in autoimmune hepatitis. *Hepatology.* 2013;57(3):1281-2.
5. de Boer YS, van Gerven NM, de Boer NK, et al. Allopurinol safely and effectively optimises thiopurine metabolites in patients with autoimmune hepatitis. *Aliment Pharmacol Ther.* 2013;37(6):640-6.
6. Friedman AB, Sparrow MP, Gibson PR. The role of thiopurine metabolites in inflammatory bowel disease and rheumatological disorders. *International journal of rheumatic diseases.* 2014;17(2):132-41.