Reply

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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[1].

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[2] suggested an association between 6-TGN concentrations above 220 pmol/8 × 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[3-5], 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[6].

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.

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