Lazarević *et al.*: *Intrinsic Activity*, 2022; **10**(Suppl. 2):A2.15
doi:10.25006/IA.10.S2-A2.15
published online: 16 September 2022

INTRINSIC ACTIVITY

26th Scientific Symposium of the Austrian Pharmacological Society

Graz, 23–24 September 2022

MEETING ABSTRACT

A2.15

Targeting gut microbiota for the individualization of thiopurine therapy of inflammatory bowel disease

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Background: Accumulating evidence shows that gut microbiota (GM) are able to influence the efficacy and toxicity of certain drugs and that treatment outcomes vary greatly among individuals due to the variability of the GM. Generally, clinical trials do not include studies aimed to examine microbiota–drug interactions, leaving knowledge gaps on important pharmacokinetic properties of orally administered drugs. This study aimed to highlight the potential of GM as key players for the implementation of a personalized approach in the thiopurine therapy of inflammatory bowel disease (IBD).

Methods: The data on the thiopurine therapy–GM interactions have been provided from a review of original scientific articles published between 2000 and 2022. The search was performed using the following keywords: 'thiopurine therapy', 'gut microbiota', 'precision medicine', and 'microbial metabolism'.

Results: Thiopurines are the most commonly used drugs for the maintenance of remission of IBD. However, considerable interindividual variability in the clinical response, with approximately 40 % of patients who are refractory to thiopurine therapy and 15–28 % experiencing adverse events, is the main reason for switching to biologics. Considering that thiopurines have a very complex metabolic pathway, the GM, with their great metabolic power, might play an important role in interindividual variability. It has already been demonstrated that *Escherichia coli*, *Enterococcus faecalis* and *Bacteroides thetaiotaomicron* are equipped with the enzymes capable of targeting the metabolic pathway of thiopurines [1]. Additionally, a recent study has confirmed that the accumulation of drugs by GM, even without biotransformation, largely affects outcomes for the majority of the studied drugs [2].

Discussion: Optimization of thiopurine therapy using a personalized treatment approach is clearly desirable before discontinuation of these drugs. Pre-treatment testing of enzymes involved in thiopurine metabolism, such as thiopurine methyltransferase (TPMT) is recommended for the therapeutic management of thiopurines by most international guidelines. Also, thiopurine treatment is monitored routinely in many laboratories by measuring metabolite concentrations in erythrocytes using high-performance liquid chromatography (HPLC) methods. Nevertheless, the drug treatment outcomes remain largely unpredictable. Therefore, further analysis of the interactions between thiopurines and GM is an important aspect which may lead to identifying novel tools for the prediction of response to the treatment and implementation of personalized IBD therapy based on GM.

Acknowledgements: This work was supported by the Ministry of Education, Science and Technological Development, Republic of Serbia (grant no. 451-03-68/2022-14/200114) and the Provincial Secretariat for Higher Education and Scientific Research of Vojvodina (grant no. 142-451-2532/2021-01).

Keywords: drug metabolism – gut microbiome – precision medicine – thiopurines

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