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Short communication

Biomarker-based thiopurine therapy for inflammatory bowel disease

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Introduction

The incidence of inflammatory bowel disease (IBD) is dramatically rising especially in western countries and there is still no cure that will lead to complete remission. Thiopurine drugs, azathioprine and 6-mercaptopurine, are often used for treating IBD and they have proven their efficacy in the maintenance remission. 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 (DeBoer et al., 2018). Optimization of the therapy using a personalized treatment approach is clearly desirable before discontinuation of these drugs. Herein, current strategies and novel tools for the individualization of thiopurine treatment of IBD will be presented.

Materials and methods

The data of different strategies for optimization of thiopurine therapy and interactions between gut microbiota (GM) and thiopurine therapy of IBD has been provided from review and original scientific articles published from 2000 to 2022. The research was performed using the following keywords: thiopurine therapy, precision medicine, therapeutic drug monitoring, TPMT enzyme, gut microbiota, microbial metabolism, drug metabolism.

Results and discussion

Pharmacogenetics

Genetic polymorphisms on enzymes involved in thiopurine metabolism, such as thiopurine methyltransferase (TPMT), inosine triphosphate pyrophosphatase (ITPase) or xanthine oxidase (XO) could affect the clinical response and be related to side effects. Anomalous genotypes of TPMT (homozygous or compound heterozygous TPMT deficiency) and NUDT15 (homozygous) have been associated with the development of severe myelotoxicity. Pre-treatment TPMT testing is recommended for the therapeutic management of thiopurines by most international guidelines. This approach allows for the reduction of thiopurine toxicities and represents a typical example of precision medicine.

Therapeutic drug monitoring

Thiopurine treatment is monitored routinely in many laboratories by measuring metabolite concentrations in erythrocytes using high-performance liquid chromatography (HPLC) method. Azathioprine and 6-mercaptopurine are prodrugs that undergo extensive metabolism generating active metabolites, 6-thioguanine nucleotides (6-TGN), and inactive, 6-methylmercaptopurine (6-MMP) and methylthioinosine (meTIMP). Meta-analyses provided evidence that TGN levels above 235 pmol/8 × 10^8 RBC make clinical efficacy more likely. Also, the determination of 6-MMP levels is important because predominant methylation

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may prevent the production of a high enough 6-TGN level and cause hepatotoxicity (6-MMP > 5700 pmol/8 × 10^8 RBC). This problem can be circumvented by co-prescription of allopurinol with azathioprine, 6-mercaptopurine dose-reduction to 25–33% of the monotherapy dose target, or a switch to thioguanine, a thiopurine drug with the less complex metabolic pathway. Even though there is a growing body of evidence that the measurement of metabolites levels provides a reasonable guide to optimal dose, its usefulness in clinical practice remains debated.

Gut microbiota – a novel biomarker of the thiopurine outcomes

A growing number of studies have demonstrated that GM is able to influence the efficacy and toxicity of orally administered drugs and that a treatment response could vary greatly among individuals due to the variability of the GM. Besides the great metabolic power of GM, a recent study has confirmed that the accumulation of drugs by GM, even without biotransformation, largely affects clinical outcomes for the majority of the studied drugs.

IBD etiology involves a role of gut dysbiosis and shifts in microbial compositions of IBD patients are associated with disease severity. Considering a very complex metabolic pathway of azathioprine and 6-mercaptopurine, GM might be a major reason for the interindividual variability among IBD patients (Lazarevic et al., 2022). 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 thiopurine drugs suggesting the involvement of GM in the clinical success of thiopurine therapy (Oancea et al., 2017). Nevertheless, the other species belonging to GM should be analyzed for the presence of enzymes required for the metabolism of thiopurines to identify biomarkers for the prediction of response to the treatment which would lead to individualized IBD therapy based on GM (Becker et al., 2022).

Conclusion

The search for factors responsible for the substantial variations in azathioprine and 6-mercaptopurine outcomes has been aided by pharmacogenetic testing and therapeutic drug monitoring. Also, the GM analysis has received particular attention as a novel tool for making clinical decisions in IBD. It would be of great importance to elucidate to what extent microbiota-thiopurines interactions contribute to the variability of the drug responsiveness. The future of IBD management will comprise different biomarkers to better predict outcomes for individual patients and to precisely tailor thiopurine therapy.

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