

SECTION 17.

PHARMACY AND PHARMACOTHERAPY

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APPLICATION OF PHARMACOGENOMICS IN STATIN THERAPY

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Statins are the most prescribed lipid-lowering medication in developed countries with more than 40 million American taking them. Pleiotropic effects of statins on cardiovascular disorders are characterized by anti-inflammatory mechanisms, improving endothelial function, inhibiting vascular smooth muscle cells proliferation, improving cardiac regeneration and anti-thrombotic activity [1, 2]. However, statins are associated with adverse effects, such as myopathy, renal and hepatic dysfunctions. [3]. Pharmacogenetic or precision medicine aims to personalize medicine, considering inter-individual genetic variability. Implementation of personalized medicine in practice may prevent occurrence of adverse events and improve the efficacy of pharmacological treatment [4]. Cytochrome P450 (CYP) enzymes affect pharmacokinetic (PK) of statins, as well as drug-drug interactions, leading to an increased risk of adverse effects and alter in statin response. Lovastatin, atorvastatin, and simvastatin (lipophilic statins) are



actively metabolized by CYP3A4 in hepatocytes. Impact of CYP3A4 polymorphisms has been investigated by different researchers. For instance, among T allele carriers of CYP3A4 * 22 gene, has been observed to have a higher bioavailability of simvastatin. CYP3A4 variants have been suggested to affect enzyme function and efficacy of statin therapy [5]. Isoforms of Uridine 50'-Diphosphoglucuronosyl transferase (UGT) enzymes (UGT1A1, UGT1A3) have been reported to be related to the PK (lactonization) of statins and drug toxicity. However, association of UGT1A1 variants (UGT1A1* 28 carriers) with atorvastatin lactone plasma concentration is controversial. Moreover, UGT1A1* 80 allele has been demonstrated to be markedly associated with a higher metabolic ratio of 2-hydroxyatorvastatin/atorvastatin and 2-hydroxyatorvastatin lactone/atorvastatin lactone. SLCO1B1 gene encodes organic anion polypeptide1B1 (OATB1B1) transporter which moderates hepatocellular uptake of drugs such as statins. SLCO1B1* 5 and SLCO1B1* 15 alleles have been documented to be associated with impaired transporter function and the occurrence of drug adverse reactions, including statin-induced myotoxicity [3, 5]. ABC gene subfamilies encode ATP-binding cassette (ABC) transporters, which involve in absorption and excretion of drugs. Simvastatin and atorvastatin have been reported to diminish the expression of ABCA1, ABCB1 and ABCC2 genes [5]. In conclusion, although gene variations of OATB1B1 and CYPs have been extensively studied, there is a lack of knowledge regarding the role of polymorphisms of genes encoding transporters like OAT-3 (Organic Anion Transporter – 3) and Sodium Taurocholate Cotransporting Polypeptide (NTCP) in response to statin therapy.

REFERENCES:

- [1] Althanoon, Z., Faisal, I.M., Ahmad, A.A. & Merkhani, M.M. (2020). Pharmacological Aspects of Statins Are Relevant to Their Structural and Physicochemical Properties. *Systematic Reviews in Pharmacy*, 11 (7), 167-171. doi:10.31838/srp.2020.7.27.
- [2] Bai, N. (2023). Researches solve mystery of how statins improve blood vessel health. *Stanford Medicine*, Retrieved from <https://med.stanford.edu/news/all-news/2023/05/statins-cardiovascular-vessels.html>.
- [3] Kee, P.S., Chin, P.K.L., Kennedy, M.A., Maggo, S.D.S. (2020). Pharmacogenetics of Statin-Induced Myotoxicity. *Frontiers in Genetics*, 11,575678. doi: 10.3389/fgene.2020.575678.
- [4] Sainz de Medrano Sainz, J.I., & Brunet Serra, M. (2023). Influence of pharmacogenetics on the diversity of response to statins associated with adverse drug reactions. *Advances in Laboratory Medicine*, 4(4), 341-352. doi: 10.1515/almed-2023-0123.
- [5] Zheng, E., Madura, P., Grandos, J., Broncel, M., Pawlos, A., Woźniak, E., et al. (2024). When the same treatment has different response: The role of pharmacogenomics in statin therapy. *Biomedicine & Pharmacotherapy*, 170,115966. doi: 10.1016/j.biopha.2023.115966.

