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Liquid Chromatography coupled with Mass Spectrometry (LC/MS) for monitoring of immunosuppressive drugs and their metabolites

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Statement of the Problem: The immunosuppressive drugs and their metabolites may often be toxic. Advances in laboratory methods enable measurement of real levels of both; a specific immunosuppressive drug and their metabolites. Older, but still widely used immunoassays yield fluctuating results and what is more, results that are often about 25-30% higher than the actual levels. On the other side, novel liquid chromatography combined with mass spectrometry (LC/MS) method obtains accurate drug level measurements.

Methodology & Theoretical Orientation: LC/MS and immunoassays (IA) were applied to assess levels of both parent drugs and its metabolites in the cohort of 834 patients after kidney transplantation (KTX), mean age: 49.13 years, median: 64.95 months after KTX. 256 (30.7%) patients were treated with cyclosporine A (CsA) and 449 (53.8%) patients were given tacrolimus (Tac).

Findings: Results of analyses of immunosuppressive drugs and their metabolites as well as differences between IA and LC/MS are presented in Table 1. Tac LC/MS to IA mean difference was 1.78 ng/ml; 89.9% of IA results overestimated real Tac levels. CsA LC/MS to IA mean was 28.8 ng/ml; 94.3% of IA results overestimated real CsA levels.

Conclusion & Significance: This preliminary study warrants the initiation of multi-centre studies of serum drug levels and metabolite pharmacokinetics. Future studies should include the analysis of large data sets, as well as long-term follow-up of patients and grafts.

Recent Publications

1. Zochowska D, Zegarska J, Hryniewiecka E, Samborska E, Jazwiec R, et al. (2016) Determination of concentrations of azathioprine metabolites 6-thioguanine and 6-methylmercaptopurine in whole blood with the use of liquid chromatography combined with mass spectrometry. Transpl Proc 48:1836–1839.
2. Hryniewiecka E, Zegarska J, Zochowska D, Jazwiec R, Borowiec R, et al. (2016) Hydroxylated, hydroxymethylated, dehydroxylated, and trihydroxylated cyclosporine metabolites can be nephrotoxic in kidney transplant recipients. Transpl Proc 48:1551–1555.
3. Zegarska J, Hryniewiecka E, Zochowska D, Samborska E, Jazwiec R, et al. (2016) Tacrolimus metabolite M-III may have nephrotoxic and myelotoxic effects and increase the incidence of infections in kidney transplant recipients. Transpl Proc 48:1539–1542.
4. Zegarska J, Hryniewiecka E, Zochowska D, Tszyrsznic W, Jazwiec R, et al. (2015) Mycophenolic acid metabolites acyl-glucuronide and glucoside affect the occurrence of infections complications and bone marrow dysfunction in liver transplant recipients. Ann Transplant 20:483–492.
5. Tszyrsznic W, Borowiec A, Pawlowska E, Jazwiec R, Zochowska D, et al. (2013) Two rapid ultra-performance liquid chromatography/tandem mass spectrometry (UPLC/MS/MS) methods with common sample pre-treatment for therapeutic monitoring of immunosuppressants compared to immunoassay. J Chromatography B 928:9–15.

Biography

Leszek Paczek, Head of the Department of Immunology, Transplant Medicine and Internal Diseases at the Warsaw Medical University, is an expert in Transplant Medicine and Nephrology. He has authored over 400 journal articles and given lectures and presentations on numerous international and national congresses. Among numerous scientific interests, he is devoted to research on the determinants of side effects and toxicity of immunosuppressive drugs with an emphasis on the role of metabolites of immunosuppressive agents. His ongoing and future projects are aimed at the development of procedures allowing the individualization of immunosuppression after solid organ transplantation.

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