**THERAPEUTIC MONITORING OF CALCINEURIN INHIBITORS: THE SUCCESS STORY STILL FACING NON-NEGLIGIBLE CHALLENGES.**

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**Background:** Calcineurin inhibitors based immunosuppressive prophylactic therapy regimen is the milestone for successful graft function sustainability today. Therapeutic monitoring of these agents (tacrolimus and cyclosporine-A) both with narrow therapeutic index and marked inter- and intra-individually variable exposure remains the most clinically applicable tool if not the best option for safer and more effective individualized dosing approach. However, there are challenges pertaining to analytical methods, sampling strategies and interpretations of results under different circumstances. **Aim:** The main objective of this contribution is to describe challenges and main pitfalls associated with methodology of monitoring and clinical evaluation of the results to guide further interventions or dose adjustment while using calcineurin inhibitors in the field of organ or tissue transplantation for event free graft function and survival. **Methods:** Certainly problematic series of cases: One adult female post lung transplantation, 1 paediatric male after kidney, and 1 paediatric male after stem-cell transplantation, respectively, were selected from clinical pharmacology consultancy requests. The Cyclosporine and Tacrolimus blood level records were analysed within timeframe of consultancy. **Results:** In all three cases, instability of concentrations was observed without clear mechanisms leading to the fluctuations of drug levels until further investigation revealed sampling time irrelevance, off-label use of drug formula, and wrong site of sampling, respectively. **Conclusions**: To overcome the present challenges, multidisciplinary reformed monitoring guidelines especially on cyclosporine-A to bind to do C2 levels independent of transplantation type is critically needed. Limited sample AUC monitoring approach may also be useful in certain conditions. In case of tacrolimus, drug formula may need attention especially in paediatric patients, where crushing a tablet is off-label use and can mislead although trough level sampling may be enough for routine monitoring. Nevertheless, pharmacogenetic and other factors accounting for variability should be considered in future to improve the state of the art.
Key words: TDM METHODS, CALCINEURIN INHIBITORS, CYCLOSPORINE-A, TACROLIMUS