Therapeutic drug monitoring of mycophenolic acid (MPA) in renal transplant pediatric patients– clinical laboratory perspective

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Background: Mycophenolic acid (MPA) is an inhibitor of IMPDH (inosine monophosphate dehydrogenase), widely used in the immunosuppressive treatment as a prodrug, mycophenolate mofetil (CellCept). Due to the variability of therapeutic response and narrow therapeutic range, the TDM (therapeutic drug monitoring) is highly recommended. The target AUC0-12 range for both adult and pediatric recipients is 30 – 60 mg×h/L.

Methods: The 25 renal transplant patients treated with MMF (concomitantly with TAC and steroids) were included in the presented study. The serum samples were collected in five-time points: C0, C0.5, C1, C1.5, and C2 via venipuncture. The TDM laboratory analyte was extracted from 0.2 mL of plasma using the LLE (liquid-liquid extraction) technique with 1,2-dichloromethane. The MPA concentration has been determined using previously validated HPLC-DAD (high-performance liquid chromatography–diode array detection) according to EMA (The European Medicines Agency) guidelines. The AUC0-12 parameter was calculated using two formulas according to LLS (limited sampling strategy) – first previously optimized in our lab (AUC0-12=8.01+6.39(C0)+0.76(C0.5)+2.69(C2)), and the second one, published in the literature (AUC0-12=8.70+4.63(C0)+1.90(C1)+1.52(C2)).

Results: The study yielded significant findings, with 75 profiles from 25 patients obtained during regular follow-up visits in the transplant outcome clinic. The trough concentration correlated poorly with the calculated AUC0-12 (0.57 and 0.49 for both formulas). The AUC0-12 ranged: 18.01 to 220.74, and 22.44 to 481.15 mg×h/L respectively. Importantly, only 44.21% of all calculated AUC0-12 were within the targeted range, underscoring the need for further research and refinement in this area.

Conclusions: Despite the high variability of individual response to MPA therapy in pediatric renal transplant recipients, the AUC0-12 estimation aids in dose adjustment, prevention of toxicity, and graft loss. Looking ahead, the introduction of the microsampling technique in regular testing of MPA therapy exposure holds promise for more accurate and efficient monitoring, potentially improving patient outcomes.

Key Words: TDM, MPA, pediatric patients, AUC, clinical pharmacokinetics