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How accurate and precise are limited sampling strategies in estimating exposure to mycophenolic acid in people with autoimmune disease? (Review)

Abd Rahman, A.N.[ab], Tett, S.E.[a], Staatz, C.E.[a]

[a]School of Pharmacy, Pharmacy Australia Centre of Excellence, University of Queensland, 20 Cornwall St, Brisbane, QLD 4102, Australia
[b]School of Pharmacy, International Islamic University of Malaysia, Kuantan, Pahang, Malaysia

Abstract

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Mycophenolic acid (MPA) is a potent immunosuppressant agent, which is increasingly being used in the treatment of patients with various autoimmune diseases. Dosing to achieve a specific target MPA area under the concentration-time curve from 0 to 12 h post-dose (AUC_{12}) is likely to lead to better treatment outcomes in patients with autoimmune disease than a standard fixed-dose strategy. This review summarizes the available published data around concentration monitoring strategies for MPA in patients with autoimmune disease and examines the accuracy and precision of methods reported to date using limited concentration-time points to estimate MPA AUC_{12}. A total of 13 studies were identified that assessed the correlation between single time points and MPA AUC_{12} and/or examined the predictive performance of limited sampling strategies in estimating MPA AUC_{12}. The majority of studies investigated mycophenolate mofetil (MMF) rather than the enteric-coated mycophenolate sodium (EC-MPS) formulation of MPA. Correlations between MPA trough concentrations and MPA AUC_{12} estimated by full concentration-time profiling ranged from 0.13 to 0.94 across ten studies, with the highest associations (r^2 = 0.90-0.94) observed in lupus nephritis patients. Correlations were generally higher in autoimmune disease patients compared with renal allograft recipients and higher after MMF compared with EC-MPS intake. Four studies investigated use of a limited sampling strategy to predict MPA AUC_{12} determined by full concentration-time profiling. Three studies used a limited sampling strategy consisting of a maximum combination of three sampling time points with the latest sample drawn 3-6 h after MMF intake, whereas the remaining study tested all combinations of sampling times. MPA AUC_{12} was best predicted when three samples were taken at pre-dose and at 1 and 3 h post-dose with a mean bias and imprecision of 0.8 and 22.6 % for multiple linear regression analysis and of -5.5 and 23.0 % for maximum a posteriori (MAP) Bayesian analysis. Although mean bias was less when data were analysed using multiple linear regression, MAP Bayesian analysis is preferable because of its flexibility with respect to sample timing. Estimation of MPA AUC_{12} following EC-MPS administration using a limited sampling strategy with samples drawn within 3 h post-dose resulted in biased and imprecise results, likely due to a longer time to reach a peak MPA concentration (t_{max}) with this formulation and more variable pharmacokinetic profiles. Inclusion of later sampling time points that capture enterohepatic recirculation and t_{max} improved the predictive performance of strategies to predict EC-MPS exposure. Given the considerable pharmacokinetic variability associated with mycophenolate therapy, limited sampling strategies may potentially help in individualizing patient dosing. However, a compromise needs to be made between the predictive performance of the strategy and its clinical feasibility. An