# VALIDATION OF LIMITED SAMPLING STRATEGY FOR ESTIMATING MYCOPHENOLIC ACID AREA UNDER THE CURVE IN HEART TRANSPLANT RECIPIENTS

**Pier Giorgio Cojutti[1], Vincenzo Tursi[2], Sandro Sponga[2], Ugolino Livi[2], Federico Pea[1], Massimo Baraldo[1]**

*[1]SOC Istituto di Farmacologia Clinica - Azienda Sanitaria Universitaria Integrata di Udine, Udine - Italy, [2]SOC Cardiochirurgia - Azienda Sanitaria Universitaria Integrata di Udine, Udine - Italy*

**Introduction:** Immunosuppressive maintenance therapy after heart transplantation usually consists of a combination of a calcineurin inhibitor (cyclosporine or tacrolimus) with mycophenolate acid (MPA) and corticosteroids. Therapeutic drug monitoring (TDM) is widely used for dose adjustments of calcineurin inhibitors in most transplant centers. On the contrary, controversies regarding its application for MPA are still present. These are essentially due to absence of appropriate platforms for MPA analysis in most laboratories and to the necessity of obtaining a MPA-area under the curve (MPA-$AUC_{0\text{-}12h}$) in order to correctly estimate drug exposure and adjust drug dosage to attain therapeutic range (30-60 mg×h/L). However, from a clinical point of view, multiple blood sample collection for MPA-$AUC_{0\text{-}12h}$ estimation is time consuming, costly and often impractical. Therefore, limited sampling strategy (LSS) for MPA-$AUC_{0\text{-}12h}$ estimation have been implemented in different population setting. In heart transplant patients, our group have already developed a 3-point LSS (MPA-$AUC_{estimated}$ = 5.568+ 0.902· $C_{1.25}$+ 2.022· $C_2$+ 4.594· $C_6$) and a 4-point LSS (MPA-$AUC_{estimated}$ = 3.8+ 1.015· $C_{1.25}$+ 1.819· $C_2$+ 1.566· $C_4$+ 3.479· $C_6$).The aim of this study was to assess the attainment of therapeutic range of MPA-$AUC_{0\text{-}12h}$ and to conduct an external validation of the developed 3-point and 4-point LSSs in a new cohort of heart transplant patients.

**Materials and methods:** This was a prospective study conducted in heart transplant patients admitted to the Department of Cardiothoracic Surgery of the University-Hospital of Udine, Italy, between January 2010 and December 2015. The present study was approved by the Regional Ethic Committee and written informed consent was obtained from all the patients.
All the subjects received the standard triple immunosuppressive therapy based mycophenolate mofetil, in combination with cyclosporine and prednisone. No other drugs known to cause pharmacokinetic interactions with MPA were concomitantly prescribed. Each patient underwent TDM of MPA at the Institute of Clinical Pharmacology. Eight blood samples were drawn at 0 (pre-dose) and at 0.5, 1.25, 2, 4, 6, 8and 12hours after the morning dose. MPA plasma concentrations were measured by means of a validated high-performance liquid chromatography (HPLC) method. MPA-$AUC_{0\text{-}12h}$ was calculated by means of the trapezoidal rule (MPA-$AUC_{reference}$) and a clinical pharmacological advice for dose adjustment was provided. Linear regression was used to assess the consistency between MPA-$AUC_{reference}$ and MPA-$AUC_{estimated}$ by means of the 3-point and 4-point nomograms.

**Results:** Thirty-four (27males) Caucasian heart transplant patients of median (min-max) age and weight of 59(22-74) years and 71.5(39-125) kg were recruited. Median (min-max) daily dose of mycophenolate mofetil was 1750 (1000-3500) mg. Median (min-max) MPA-$AUC_{reference}$ was 45.3(12.0-131.0) mg×h/L. Only 56% (19/34) patients had MPA-$AUC_{reference}$ in therapeutic range. Conversely, underexposure was observed in 26% (9/34) patients and overexposure in 18% (6/34) patients.
A high correlation was observed between MPA-$AUC_{reference}$ and MPA-$AUC_{estimated}$ by means of the 3-point LSS ($r=0.92$, 95%CI 0.84-0.95, $p<0.001$) and 4-point LSS ($r=0.93$, 95%CI 0.86-0.96, $p<0.001$).

**Conclusion:** This study confirms the high variability of MPA-$AUC_{0\text{-}12h}$ in heart transplant patients and supports the use of TDM for individualizing drug dosages in this population. The developed LSSs for MPA-$AUC_{0\text{-}12h}$ estimation seems to be both statistically robust and time sparing and may be useful in routine clinical practice to rapidly and effectively personalize MPA exposure.