Mycophenolic Acid AUC estimation in patients with lupus nephritis using an algorithm validated in an heart transplanted population

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The standard of care for lupus nephritis is represented by cyclophosphamide and steroids, but the occurrence of serious drug-related adverse events is commonplace. Mycophenolic acid (MPA) showed a similar efficacy and a less toxic profile than cyclophosphamide and consequently has recently replaced this latter drug as the first-line treatment for proliferative lupus nephritis.

However, the pharmacokinetic of MPA is characterized by a wide intra- and inter-individual variability, and therapeutic drug monitoring (TDM) has been advocated as a useful tool in optimizing MPA dosing regimen.

TDM of MPA has been initially adopted for preventing organ rejection following transplantation: in this setting, MPA area under the curve (MPA-AUC_{0-12h}) has demonstrated to be a better predictor of rejection in both renal and cardiac transplantation with respect to trough concentration (C_0), with a therapeutic range between 30 and 60 mg*h/L.

From a clinical point of view, MPA-AUC_{0-12h} determination is an important burden both for the patients and for the medical staff; consequently, different limited sampling strategies (LSSs) for MPA-AUC_{0-12h} estimation have been studied and validated in renal, liver and heart transplanted patients. Two of these LSSs are currently used at our University-Hospital for routine MPA-AUC_{0-12h} calculation in heart transplanted patients: $AUC = 5.568 + 0.902*C_{1.25} + 2.022*C_2 + 4.594*C_6$ or, the preferred formula, $AUC = 3.800 + 1.015*C_{1.25} + 1.819*C_2 + 1.566*C_4 + 3.479*C_6$.

Considering that some authors have recently hypothesized that an $AUC_{0-12h} > 45$ mg * h /L allows a better response even in lupus nephritis, the aim of this study is to verify whether the LSSs for MPA-AUC_{0-12h} estimation, validated in heart transplanted patients, might be suitable for MPA-AUC_{0-12h} estimation in rheumatological patients affected by lupus nephritis.

In 5 rheumatological patients (mean age 34.2±10.3 yrs) with lupus nephritis, receiving concomitant steroid therapy and whose clinical conditions were deemed stable, 31 MPA full AUC_{0-12h} profiles have been collected. The mean MPA dose was 2.2±0.8 g/die.

Blood samples were collected in EDTA tubes at 0 (pre-dose), 0.5, 1.25, 2, 4, 6, 8 and 12 hour post-dose, after the morning dose. Plasma MPA concentrations have been measured by a validated high performance liquid chromatography (HPLC) method. Full MPA-AUC_{0-12h} values were calculated using Winnonlin version 1.1.

These full MPA-AUC_{0-12} profiles were compared to those obtained using the two LSS algorithms at the analysis of variance.

The mean ± standard deviation of MPA-AUC_{0-12h} calculated with the standard sampling strategy and using the two proposed formula were 77.5±26.5, 58.9±18.5 and 60.9±19.5 mg*h /L respectively. A statistically significant difference between the three method emerged (p = 0.011).

This study demonstrates that the MPA-AUC_{0-12h} estimation in rheumatological patients cannot be carried out using LSSs validated in heart transplanted subjects. Therefore, LSS algorithms have to be formulated and validated specifically for this population.