RENAL TRANSPLANTATION. CLINICAL - 2

SP838 PROSPECTIVE, 6 MONTH, OPEN LABEL, CONVERSION STUDY FROM MYCOPHENOLATE MOFETIL TO MYCOPHENOLIC ACID EVALUATING THE SEVERITY OF GASTRO-INTESTINAL SYMPTOMS AND MYCOPHENOLIC ACID URINARY METABOLITE AS A SURROGATE MARKER OF PLASMATIC AREA UNDER THE CURVE

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Introduction and Aims: Treatment with mycophenolate mofetil (MMF) in the kidney transplant population often results in adverse gastro-intestinal (GI) events, which can lead to dose reductions that in turn can increase the risk of rejection. Many studies have shown that MPA has a better GI side effect profile than MMF for the first weeks up to three months after initiation of treatment but we do not know if the situation remains the same in the long term. Currently, the measurement of 12 hours plasmatic MPA area under the curve (AUC) is the most accurate way to determine MPA exposure in kidney transplant patients. However, obtaining hourly blood samples for 12 hours is highly undesirable to the patient and impractical for the medical staff. MPA glucuronide (MPAG) is the most abundant metabolite of MPA and its route of elimination is via the urine. The quantity of MPAG in the urine, if shown to correlate with plasma levels of MPA, could serve as a surrogate marker for plasmatic MPA AUC.

Methods: Open label single center study of 56 stable kidney transplant patients receiving MMF at the time of screening. The study took place between September 2007 and December 2013. All patients underwent an equimolar conversion to MPA. The gastrointestinal symptom rating scale (GSRS) questionnaire is a 15-item instrument assessing impact of GI symptoms as perceived by the patient and based on a range of 1 (no discomfort) to 7 (very severe discomfort). The GSRS consists of 5 dimensions measuring reflux, diarrhea, constipation, abdominal pain and indigestion. Patients filled the questionnaire at study entry, month 1, 3 and 6. Thirteen of the 56 patients were enrolled in the pharmacokinetics sub-study. These patients had 12 hours plasmatic MPA AUC and 12 hours urine content of MPAG measured by high performance liquid chromatography at month 1 and 3 after conversion.

Results: The score of each dimension of the GSRS questionnaire decreases significantly as soon as month 1 after conversion and this improvement stays statistically significant up to 6 months when compared with baseline. The diarrhea dimension goes from a mean of 4.7 points before conversion to a mean of 2.7 points at 6 months, which translates clinically from « moderately severe » diarrhea to a « mild discomfort » over time. Also, the total GSRS score drops almost 5 points over 6 months (p<0.0001). 85.2% of the patients could tolerate their initial or a higher dose of MPA during the whole course of the study. The correlation between the urinary amount of MPAG excreted in 12 hours and the 12 hours plasmatic MPA AUC was r=0.82 (p=0.001) at month 1 and r=0.87 (p=0.0002) at month 3. The correlations remained statistically significant when the urinary excretion of MPAG was corrected for the glomerular filtration rate: r=0.93 (p<0.0001) at month 1 and r=0.84 (p=0.0004) at month 3. The kidney function and the cell blood counts were stable throughout the study.

Conclusions: In our study, the conversion from MMF to MPA in stable kidney transplant recipients, to lower GI side effects, seems to be an effective and safe strategy. The improvement is significant already at 1 month after conversion and remains clinically important at 6 months. Furthermore, measuring the urinary MPAG excretion in a twelve-hour urine collection could be a practical and accurate tool to better estimate the plasmatic MPA AUC without multiple venous punctures for the patient and the monopolization of nursing resources for many hours.