Impact of Therapeutic Drug Monitoring of Mycophenolate Mofetil in Patients with Lupus Nephritis: A Randomized Clinical Trial

29/01/2026

Randomized clinical trial, blinded to participants, to be conducted with patients treated at the Rheumatology Outpatient Clinic of the University Hospital of the Federal University of Maranhão (HU-UFMA) by a clinical pharmacist/researcher from the Clinical Pharmacy Unit (UFCLI) and a rheumatologist. The Clinical Research Center (CEPEC/UFMA) and the Clinical Analysis Laboratory of HU-UFMA will serve as reference sites for patient blood collection and for performing and analyzing laboratory tests, respectively. Serum MPA levels will be measured by a reference laboratory. The study will be conducted with patients diagnosed with lupus nephritis who are receiving mycophenolate mofetil through the Specialized Component of Pharmaceutical Services of the Brazilian Public Health System (SUS), over a 12-month period.

General objective is determine whether the implementation of therapeutic drug monitoring of mycophenolate mofetil (TDM-guided) in patients with lupus nephritis results in a higher rate of renal remission over 12 months compared to standard clinical management.

Specific objectives is to evaluate secondary clinical outcomes of lupus nephritis (LN), such as the rate of patients achieving renal remission, partial remission and relapse rates, rate of non-response, number of dose adjustments, and mean MMF dose adjusted over 12 months. To determine the association between C0 concentration and reduction in proteinuria/estimated Glomerular Filtration Rate (eGFR), as well as adverse events. To determine the occurrence of adverse effects, hospitalizations, rate of temporary or permanent MMF discontinuation due to toxicity, and medication adherence.

To evaluate the impact of the clinical pharmacist's role in the MMF dose adjustment process guided by TDM, considering dose appropriateness, achievement of the target therapeutic range, and patients' clinical outcomes, in addition to promoting health education and treatment adherence.

Based on clinical records from HU-UFMA and FEME/MA, it is estimated that approximately 187 patients diagnosed with lupus nephritis (classes III–V) and receiving mycophenolate mofetil (MMF) are currently under specialized outpatient follow-up. However, according to the sample size calculation described below, 50 participants will be required in each group, totaling 100 randomized patients (control group and intervention group). The sample will consist of consecutive patients who meet the eligibility criteria and agree to participate by signing the informed consent form. Recruitment will occur continuously until the established sample size is reached.

The sample size calculation was based on comparing the proportion of patients achieving renal remission at 12 months in the control group (MMF with usual management) versus the intervention group (MMF with therapeutic drug monitoring of mycophenolic acid [MPA] and dose adjustment guided by TDM). A remission rate of 60% was assumed for the control group and 80% for the intervention group, resulting in an expected difference of 20 percentage points between proportions.

Assuming a significance level of 10% ($\alpha = 0.10$) and statistical power of 70% ($\beta = 0.30$), the minimum required sample size was 49 participants per group, calculated using the formula for comparison of two independent proportions. To account for potential losses to follow-up (up to 10%) and ensure robustness of the analysis, the value was rounded up to 50 participants per group, totaling 100 patients.

As this is a single-center, randomized clinical trial with an exploratory design, the sample parameters were defined considering operational feasibility and focusing on generating estimates to support future multicenter studies with greater statistical power.

Inclusion criteria:
1. Adults aged ≥18 years, of both sexes
2. Diagnosis of systemic lupus erythematosus (SLE) according to the ACR criteria, with at least four criteria present for the diagnosis of SLE, and active lupus nephritis (class III–V) documented by renal biopsy with histological classification within the last 6 months or presence of urine protein-to-creatinine ratio (UPCR > 0.5) or 24-hour proteinuria (>500 mg)
3. Use of mycophenolate mofetil (MMF) in the maintenance phase within the first 3 months
4. Residents of the municipalities of São Luís, São José de Ribamar, and Paço do Lumiar, located in the Metropolitan Region of Greater São Luís

Exclusion criteria:
1. Individuals with contraindications to MMF (known hypersensitivity, pregnancy, or breastfeeding)
2. Active severe infection (e.g., tuberculosis, sepsis)
3. Unstable renal replacement therapy and severe hepatic failure
4. Use of investigational drugs
5. Concomitant use of drugs that strongly modify pharmacokinetics (PK) without the possibility of adjustment, such as rifampicin.

Participants will be recruited through the electronic medical record system (AGHUx) to identify patients followed at the rheumatology outpatient clinic at HU-UFMA, as well as through reports of patients receiving MMF dispensed by the Specialized Medication Pharmacy (FEME) of the State of Maranhão between January 2026 and December 2027.

Randomization: Participants will be randomly assigned (1:1) in blocks of four to receive either TDM-guided MMF therapy or standard MMF treatment. An independent researcher will perform group allocation and generate the randomization sequence using a computer-based algorithm. Observers will be blinded to group allocation through the use of sealed, opaque envelopes to ensure allocation concealment. Data analysts will not be involved in participant assessment or treatment and will remain blinded to group allocation until the data analysis phase.

Intervention Protocol

The study will be conducted according to the intervention protocol described below:

Serum MPA (C0) concentrations will be measured at three time points (T1, T2, and T5), ensuring reduced operational costs and lower participant burden while maintaining the ability to assess pharmacological exposure.

Intervention group (TDM-guided): Serum MPA (C0) levels will be measured at three time points (T1, T2, and T5). Between these visits, outpatient clinical evaluations (T1–T5) will be conducted without bioanalytical MPA sampling, allowing continuous clinical follow-up with reduced participant burden and optimized resource use.

Control group: Participants will receive MMF according to the Brazilian Ministry of Health protocol for lupus nephritis, with quarterly clinical evaluations (T1–T5) and no therapeutic drug monitoring of MPA.

The therapeutic C0 target will be $\geq$ 2.5 mg/L, according to the literature for patients in the maintenance phase of MMF therapy. Dose adjustments will follow a standardized protocol, with titration intervals between 25% and 50%, depending on clinical tolerability and the occurrence of adverse events.

Researcher–Participant Contact and Clinical Oversight

The researcher and/or research assistant may contact the participant whenever there is suspicion of toxicity or therapeutic failure, according to the evaluation of MMF serum monitoring, and to provide guidance regarding drug therapy and sample collection for scheduled TDM during the study.

Recommendations or interventions proposed by the clinical pharmacist/researcher will be discussed with the responsible rheumatologist before any dose modification. Dose adjustments will be documented in a standardized form, including: MMF C0 concentration, current dose and recommended dose, technical justification, prescriber approval with the new dosage, and the planned date for reassessment, which will be communicated to the patient according to the prescriber's decision in the rheumatology outpatient clinic and the study design.

Primary Clinical Outcome

The primary outcome will be the proportion of patients achieving renal remission at 12 months. For analysis purposes, remission will be treated as a dichotomous variable: (a) renal remission (complete or partial), or (b) absence of remission.

This approach allows a more straightforward statistical analysis and greater stability in estimating the effect of the intervention.

Clinical assessments of remission will occur at four quarterly time points (T2–T5), while MPA monitoring will occur at three time points: 15 days after signing the informed consent form (T1), 3 months (T2), and 12 months (T5).

a) The complete and partial clinical remission of LN will be available for:

- Creatinine (mg/dL)
- Change in 24-hour proteinuria (g/g) to <25% of the baseline value or in the 24-hour urine protein-to-creatinine ratio (UPCR) at 3 months
- Change in 24-hour proteinuria (g/g) to <50% of the baseline value or in the 24-hour urine protein-to-creatinine ratio (UPCR) at 6 months
- Change in proteinuria to <0.8 g/24 h at 12 months
- Change in 24-hour proteinuria (g/g) to ≤50% of the baseline value or in the 24-hour urine protein-to-creatinine ratio (UPCR) at 6-12 months
- Improvement or stabilization of eGFR (±10%–15% of baseline) within 6–12 months after treatment initiation

b) No response: Defined as no complete or partial renal response after 6–12 months of therapy initiation.

Secondary Clinical Outcomes

The secondary outcomes to be evaluated in this clinical trial include: MPA concentration (C0) during follow-up (T1, T2, T5), Adverse events related to MMF, Hospitalizations related to lupus nephritis and Medication adherence, assessed by the Brief Medication Questionnaire (BMQ). Additional hemostatic and inflammatory variables may be analyzed in an exploratory approach (substudy), depending on operational feasibility and the availability of complete samples.

Inclusion criteria:

- Adults aged ≥18 years, of both sexes
- Diagnosis of systemic lupus erythematosus (SLE) according to the ACR criteria, with at least four criteria present for the diagnosis of SLE, and active lupus nephritis (class III–V) documented by renal biopsy with histological classification within the last 6 months or presence of urine protein-to-creatinine ratio (UPCR > 0.5) or 24-hour proteinuria (>500 mg)

- Use of mycophenolate mofetil (MMF) in the maintenance phase within the first 3 months
- Residents of the municipalities of São Luís, São José de Ribamar, and Paço do Lumiar, located in the Metropolitan Region of Greater São Luís

Exclusion criteria:

- Individuals with contraindications to MMF (known hypersensitivity, pregnancy, or breastfeeding)
- Active severe infection (e.g., tuberculosis, sepsis)
- Unstable renal replacement therapy and severe hepatic failure
- Use of investigational drugs
- Concomitant use of drugs that strongly modify pharmacokinetics (PK) without the possibility of adjustment, such as rifampicin.