SIROLIMUS TROUGH LEVELS IMPACT CHRONIC GRAFT-VERSUS-HOST DISEASE INCIDENCE

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Introduction

Sirolimus is a valid alternative to calcineurin inhibitors when associated with post-transplant cyclophosphamide (**PTCY**) as graft-versus host disease (GVHD) prophylaxis in hematopoietic stem cell transplant (HSCT). However, little is known about the impact of **sirolimus trough levels** (STL) on transplant outcomes, and particularly chronic GVHD (cGVHD).

Aims

To explore the relationship between STL during the first 90 days after transplant and cumulative incidence (CI) of moderate to severe cGVHD

Methods

- Retrospective, single-center study (Hospital Universitari i Politècnic La Fe, Valencia)
- **Inclusion criteria**:
  - Adults with hematologic malignancies undergoing allo-HSCT (January 2017 – December 2024)
  - GVHD prophylaxis with PTCY + sirolimus + mycophenolate mofetil
  - Sirolimus not suspended before day +90
- **STL target**: 5–15 ng/mL until day +90; first measured at day +8
- **Assessment of sirolimus exposure**:
  - Mean STL across different time periods
  - Intraindividual coefficient of variation
- **Primary endpoints**:
  - Impact of STL on moderate-severe cGVHD
  - Optimal SLT threshold predicting cGVHD

	No cGVHD (mean ± SD; 95% CI)	cGVHD (mean ± SD; 95% CI)	p
ICV	51.4 ± 17.8	49.6 ± 15.6	0.43
mSTL from +8 to +30	10 ± 3	10.3 ± 3.1	0.35
mSTL from +30 to +60	10.6 ± 4.1	10.6 ± 3.5	0.99
mSTL from +60 to +90	9.6 ± 3.8	8.3 ± 3.6	**0.011**
mSTL from +8 to +90	10 ± 2.4	9.9 ± 2	0.78

Table 1. Comparison of sirolimus exposure between patients with and without chronic graft-versus-host disease (cGVHD); Student's t-test. CI = confidence interval, ICV = intraindividual coefficient of variation, mSTL = mean sirolimus trough levels, SD = standard deviation

Results

- 318 patients were included in the analysis
- 73 (23%) developed cGVHD
- **Mean STL from day +60 to +90** significantly differed between patients with and without cGVHD (8.3±3.6 vs. 9.6±3.8 ng/mL, p=0.011)
- **Optimal STL cutoff** was **5.5 ng/mL**, showing 26.7% sensitivity and 90.6% specificity
- Patients with STL above 5.5 ng/mL had a **significantly lower CI of cGVHD** (23.7% vs. 51.9%, p <0.001)

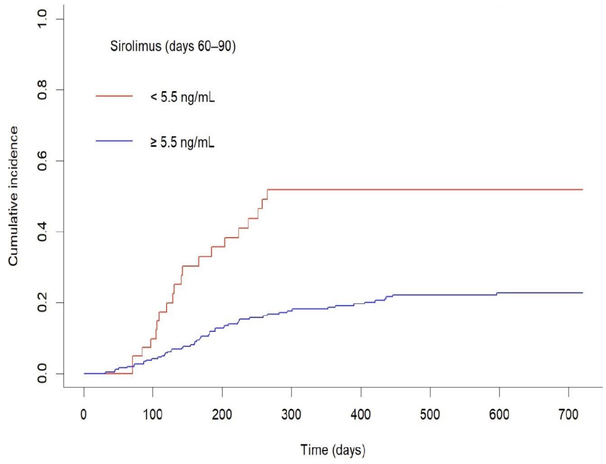


Figure 1. Cumulative incidence of graft-versus-host disease by sirolimus group. Relapse and death were considered competing risks

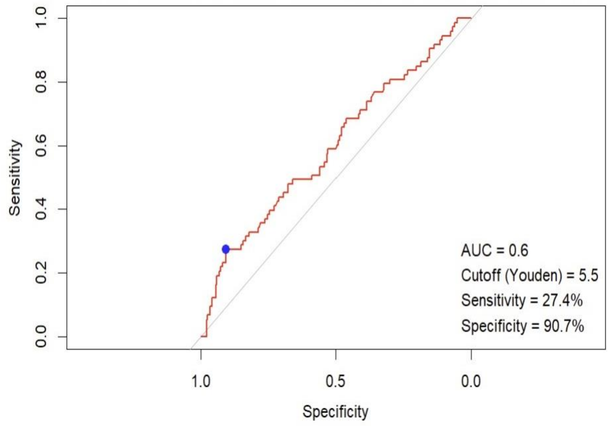


Figure 2. Receiver operating characteristic (ROC) curve: mean sirolimus trough levels (days +60 to +90) vs. chronic graft-versus-host disease occurrence.

Conclusions

- Higher sirolimus exposure between days +60 to +90 post-transplant is associated with a reduced risk of moderate to severe cGVHD
- A threshold of 5.5 ng/mL may be a clinically useful benchmark.
- Prospective studies with multivariate analyses are warranted to validate these findings