ISHLT JOURNAL WATCH January 2026 | Pharmacy

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Outcomes and Tolerability of Early Mammalian Target of Rapamycin Inhibitor Initiation for Renal Sparing in Heart Transplant Recipients

Marcotte A, Rikard R, Castor C, Meilhac M, et al. *Clinical Transplantation* 27 Oct 2025;39(11):e70364. | DOI: 10.1111/ctr.70364

Study Highlights

Objective: To evaluate the impact of early mammalian target of rapamycin inhibitor (mTORi) initiation in combination with reduced tacrolimus (TAC) on renal function and graft outcomes in heart transplant recipients (HTRs).

Methods:

- Single-center, retrospective cohort study
- Included adult HTRs transplanted 1/2018 - 12/2023
- Excluded dual organ transplant (txp), repeat txp, cyclosporine or belatacept-based immunosuppression (IS)
- Compared HTRs who initiated an mTORi within the first-year post-txp vs. remained on standard of care (SOC) IS

Results:

- Thirty HTRs in the mTORi group were compared to 51 HTRs in the SOC group with similar baseline characteristics
- Majority (63%) HTRs were initiated on an mTORi due to renal dysfunction at a median of 183 days post-txp
- Median sirolimus troughs from month (mo) 6-24 post-txp: 4.3-5.4 ng/mL. Table 1 summarized IS regimens
- Percent change in eGFR from mo 6-24 post-txp between the mTOR and SOC groups: 36.8% vs. 11.0%, p = 0.03
- Zero HTRs in the mTORi group vs. 7 HTRs in the SOC group developed cardiac allograft vasculopathy (CAV) by 24 mo (p = 0.03). Rejection rates were similar between groups

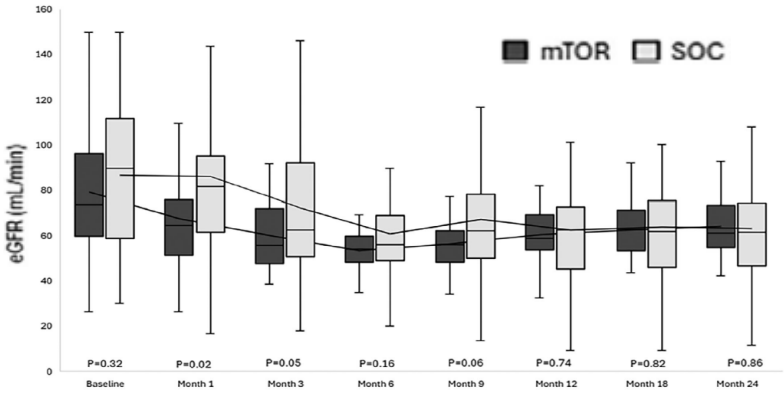
Conclusions: Early mTORi initiation with reduced TAC was associated with renal benefits and CAV prevention without increasing rejection risk.

Table 1. Immunosuppression

Tacrolimus trough (ng/mL), median (IQR)			
1 month	11.4 (7.7)	9.5 (4.3)	0.22
6 month	7.8 (4.1)	8.0 (3.8)	0.05
9 month	4.8 (1.7)	8.0 (4.4)	<0.001
12 month	4.8 (2.4)	7.4 (4.2)	<0.001
24 month	4.9 (1.8)	7.0 (3.5)	<0.001
Mycophenolate dose (mg), median (IQR)			
1 month	2000 (0)	2000 (0)	0.21
6 month	1000 (1500)	1000 (1500)	0.28
9 month	0 (1000)	500 (1500)	0.01
12 month	0 (0)	500 (1500)	0.01
24 month	0 (0)	500 (1500)	0.02

Prednisone dose is similar between two groups after 1 month

Figure 1. eGFR trajectory post-transplant



Reviewer's Comments

- mTORi-based IS regimens without calcineurin inhibitors (CNI) have demonstrated superior renal function when compared to CNI-based IS regimens
- However, CNI free IS regimens are associated with an increased risk of rejection
- Minimal literature has evaluated low dose CNI especially TAC plus mTORi on renal function and graft outcomes. This study demonstrated the utility of early mTORi initiation with reduced TAC to preserve renal function without increasing rejection risk
- This study also supports the CAV benefit with early initiation of an mTORi

Limitations

- The study is a single-center retrospective study with a relatively small sample size. This reduces the statistical power to detect small differences in rejection rate.
- HTRs initiating an mTORi greater than 1-year post-txp were stratified to the SOC group (7/51, 14%)
- The majority of HTRs were chronic kidney disease stage 3b or better
- Future research is needed to demonstrate the long-term renal benefit of low dose TAC plus mTORi IS regimen

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NUDT15 Genetic Polymorphism as a Risk Factor for Early Neutropenia During Valganciclovir Prophylaxis in Lung Transplant Patients

Katsube Y, Umemura K, Urabe Y, Ono M, et al. *Transplant Infectious Disease* 2025 18 Aug;27(6):e70108. | DOI: 10.1111/tid.70108

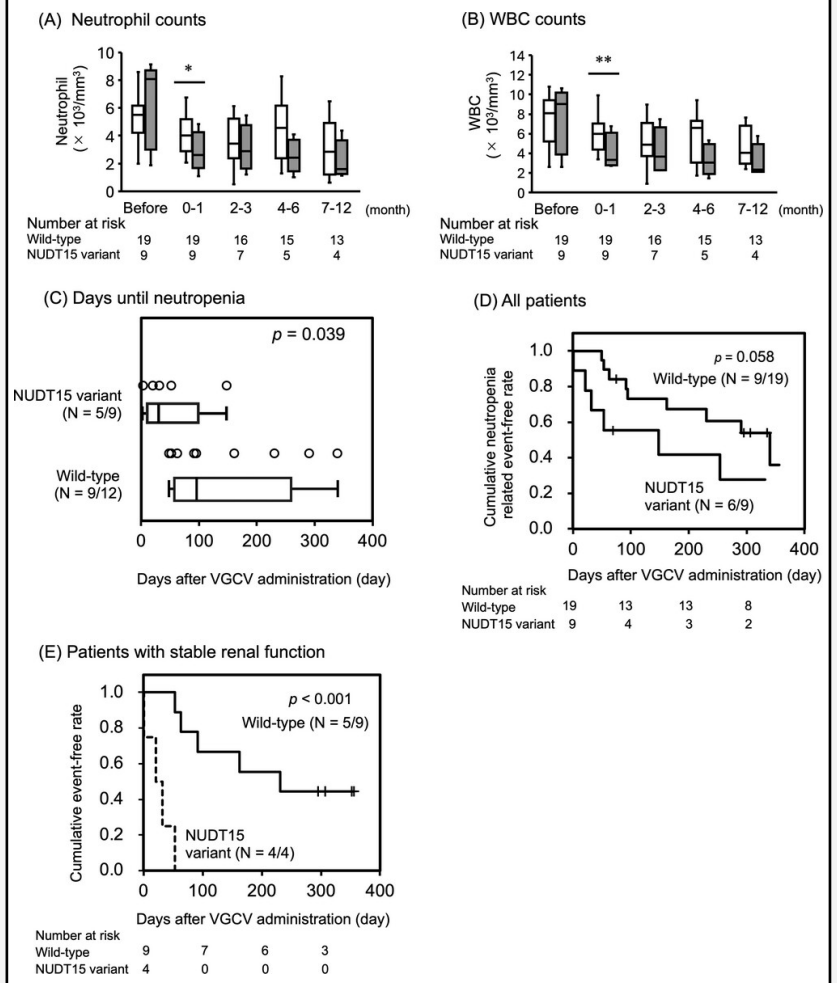
Study Highlights

Objective: Evaluate if NUDT15 genotype predicts development of neutropenia in lung transplant recipients receiving valganciclovir for prophylaxis of cytomegalovirus (CMV). NUDT15 has a critical role in dephosphorylation of intracellular ganciclovir triphosphate, the active metabolite.

Methods: Single center, retrospective, observational, cohort study that included patients receiving lung transplant between July 2021 and October 2024 who were given valganciclovir (VGC) for CMV prophylaxis. Prophylaxis utilized intravenous ganciclovir (GCV) 5 mg/kg twice daily for 3 weeks followed by VGC 900 mg once daily. High risk patients received prophylaxis for as long as tolerated.

Results: A total of 28 patients were included in final analysis. Nine patients carried at least 1 mutation. Median absolute neutrophil count (ANC) was lower in carriers during the first month after, but not long-term. Time to first episode of neutropenia was faster among carriers (median 32 (4-148) vs 96 (49-340) days, $p < 0.05$). Overall incidence of neutropenia was not significantly different on Kaplan-Meier analysis. NUDT15 genotype was not associated with GCV trough level. Subgroup analysis of patients with stable renal function found that those with NUDT15-variant had higher rates of neutropenia compared to wild-type (4/4 vs 5/9; $p < 0.001$).

Conclusions: NUDT15 genotype may contribute development of neutropenia on valganciclovir, though additional studies with larger and more diverse populations are needed.



Reviewer's Comments

- Ability to predict intolerance to GCV or VGC is of significant interest and could help prioritize patients into alternative modalities to minimize morbidity
- ANC and WBC were significantly lower in carriers of NUDT15 polymorphisms during the first month after transplant when patients received treatment intensity GCV for 3 weeks
- NUDT15 genotyping can be costly compared to more readily available activity assays. Future studies could include activity assay data to determine if these can discriminate risk

Limitations

- Study included Japanese patients which may limit external validity to more heterogeneous populations
- It was unclear how long most patients received VGC over the course of the first year after transplant. 25% of patients included were high-risk mismatch
- Small sample size likely hindered evaluation of endpoints, particularly exploration of renal function as a covariate
- Serum or plasma ganciclovir levels may not accurately reflect gene-drug interaction as mutations in NUDT15 are predicted to increase intracellular concentrations of the active metabolite

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Daratumumab monotherapy as a desensitization strategy prior to cardiac transplantation

Crespo-Diaz RJ, daSilva-deAbreu AJ, Rosenbaum AN, Bernard SA, et al. *JHLT* 2025 Aug;44(8):1300-1306. | DOI: 10.1016/j.healun.2025.01.021

Study Highlights

Objective: Human leukocyte antigen (HLA) sensitization is a significant contributor to increased waitlist time *and* mortality in heart transplant candidates. While desensitization has become a popular strategy in modern cardiac transplantation, heterogenous response to conventional therapies remains a major limitation. Daratumumab (DARA) is a human IgG1κ CD38 monoclonal antibody that induces apoptosis of CD38+ immune cells. The objective of this study was to demonstrate the safety and efficacy of DARA monotherapy for desensitization in highly sensitized patients awaiting heart transplant.

Methods: This was a prospective, open-label trial of six highly sensitized patients with a calculated panel reactive antibody >50% who were eligible for heart transplant. They were given weekly doses of 1,800 mg DARA and 30,000 units hyaluronidase via subcutaneous injection for a planned duration of eight weeks. The primary endpoint was the extent to which DARA lowered HLA antibodies.

Results: Three patients completed eight weeks of DARA, and three received partial treatment. Most patients experienced a decrease in HLA class I and II antibodies, with variable extent and timing of response. The most significant decrease was in patients who completed 8 weeks of therapy. DARA was well tolerated with patients experiencing only grade 1 to 2 reactions including gastrointestinal upset, fatigue, and myalgias. Five of the six patients were successfully transplanted and have maintained normal graft function without any episodes of antibody-mediated rejection for up to twelve months posttransplant.

Conclusions: DARA monotherapy may provide an effective and tolerable approach to desensitization in highly sensitized heart transplant candidates who are precluded from conventional therapies.

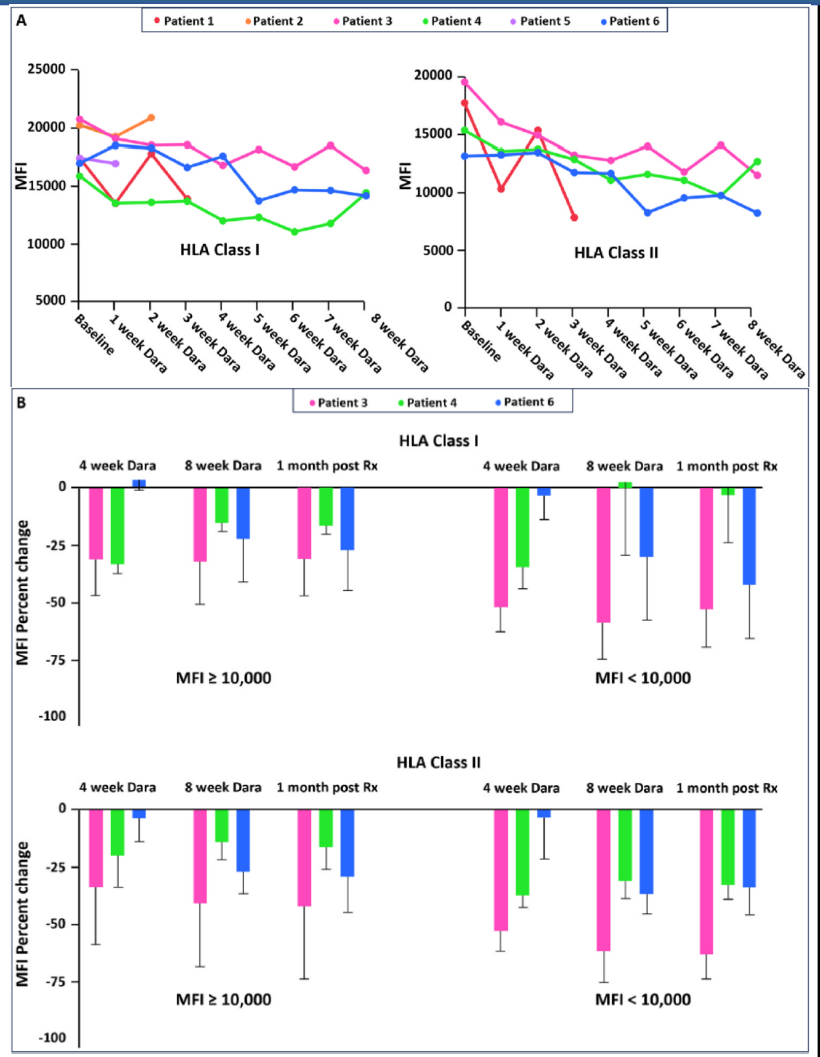

Figure 2. Effect of daratumumab on HLA antibody levels. A. Change in MFI over 8-week duration of therapy. B. Percentage change in MFI from baseline to 4 weeks, 8 weeks, and 1-month post-treatment.

Reviewer's Comments

- This prospective study contributes to a growing body of evidence supporting DARA as a feasible desensitization strategy in heart transplant candidates
- The authors demonstrate that DARA may significantly reduce class I and class II antibody levels, even at high titers, with sustained response at one-month post-treatment. Furthermore, at least one patient demonstrated a strong enough response to proceed with transplant after just a few doses of DARA. All six patients tolerated DARA, only experiencing mild adverse effects not warranting discontinuation.
- The three patients included for analysis did not exhibit graft dysfunction or rejection for up to 12 months posttransplant

Limitations

- The single center, small sample size nature of this study limits generalizability to a broader cohort
- Potential confounders were not addressed in the posttransplant analysis such as maintenance immunosuppression at those time points and posttransplant antibody trends that could have warranted pre-emptive rejection treatment
- There was an opportunity to assess post-DARA antibody trends in the only patient still awaiting transplant to determine at what point and to what degree they may rebound after completing treatment
- Future studies should aim to elucidate optimal DARA dosing, duration, and place in therapy for desensitization of heart transplant candidates