ISHLT JOURNAL WATCH
August 2024 | Pharmacy

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Utility of a fusion protein T-cell co-stimulation blocker Belatacept in heart transplant recipients: Real world experience from a high-volume center

Oren, et al. *Clinical Transplantation* 2024 | doi.org/10.1111/ctr.15251

Study Highlights

Objective: Aimed to determine the efficacy, safety, and complications of belatacept (BTC) in post-heart transplant (OHT) recipients at a high-volume center.

Methods: Retrospective, single center, cohort evaluating all heart transplant recipients who received BTC as part of their maintenance immunosuppression. Outcomes assessed: renal function, graft function, graft rejection, and mortality.

Results: 21 patients were included. BTC was initiated at a median 22.6 months post-transplant; most commonly added for donor specific antibodies (DSAs) (66.6%), and renal dysfunction (23.8%). After belatacept initiation, majority of heart transplant recipients remained on tacrolimus (85.7%). Graft function remained stable. Only 1 patient experienced rejection. 76.2% patients had an improvement in SCr (median 1.58 to 1.45) over 12 months; this was not statistically significant. 11 (52.4%) patients developed an infection.

Conclusion: BTC in combination with tacrolimus seemed to preserve renal and heart graft function

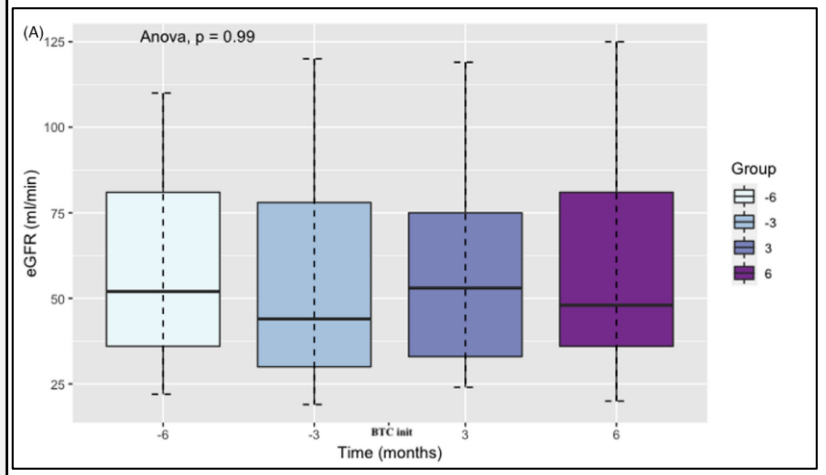
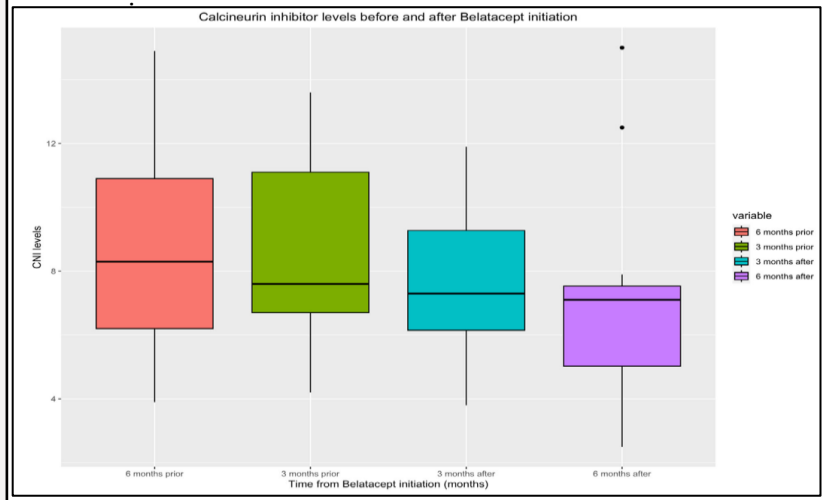


Figure 1: eGFR 3 and 6 months before and after BTC conversion

Figure 2: CNI levels 3 and 6 month before and after BTC



Reviewer's Comments

- High use of calcineurin inhibitors (CNI) with belatacept.
- Lower rejection rates which differ from previously published work (Launay et al. *Am J Transplant*. 2020). Likely influenced by higher CNI use.
- High use of CNI likely influenced the non-statistically significant improvement in renal function.
- No mention of changes in circulating DSAs despite this being the most common indication for BTC.
- Potential role of using BTC with CNI to stabilize renal function and preserve graft function in OHT.

Limitations

- This cohort was not matched to a different cohort to assess differences in outcomes of BTC vs no BTC.
- Heterogenous group in terms of indication for BT, immunologic risk, and management of other immunosuppression (ie: other immunosuppression dosing and goal troughs).

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Tacrolimus Variability and Clinical Outcomes in the Early Post-lung Transplantation Period: Oral Versus Continuous Intravenous Administration

van Dommelen et al. *Clin Pharmacokinet 2024*| https://doi.org/10.1007/s40262-024-01368-1

Study Highlights

Objective: This study compares the variability in tacrolimus blood levels and related clinical outcomes between oral and continuous intravenous administration in the first 14 days following lung transplantation.

Methods: Retrospective cohort study of 522 lung transplant patients. Patients were divided into oral (224) and intravenous (298) tacrolimus groups. Tacrolimus concentrations were analyzed using liquid chromatography-mass spectrometry (LC-MS/MS) to ensure accuracy.

Key Findings:

- **Intrapatient Variability (IPV%)**: Oral administration resulted in higher IPV% (27.2%) compared to intravenous administration (16.4%).
- **Time within Therapeutic Range (TTR%)**: Oral administration had lower TTR% (39.6%) than intravenous (46.9%).
- **Acute Kidney Injury (AKI)**: No significant difference in overall AKI incidence, though stage 1 AKI was more frequent in the oral group.
- **Acute Rejection**: Slightly higher rejection rates in the oral group, but not statistically significant.
- **ICU Outcomes**: Similar ICU length of stay and mortality rates between the two groups.

Conclusion: Continuous intravenous administration of tacrolimus in the early post-transplant period leads to more stable blood levels compared to oral administration. This method can reduce variability-related risks without increasing AKI or rejection rates, suggesting it as a preferable approach immediately after lung transplantation.

Figure 1. Representation of the calculation of the time in- and outside of the therapeutic range of tacrolimus. The green, grey, and yellow areas represent the time within, above, and beneath the therapeutic range, respectively. LuTx lung transplantation

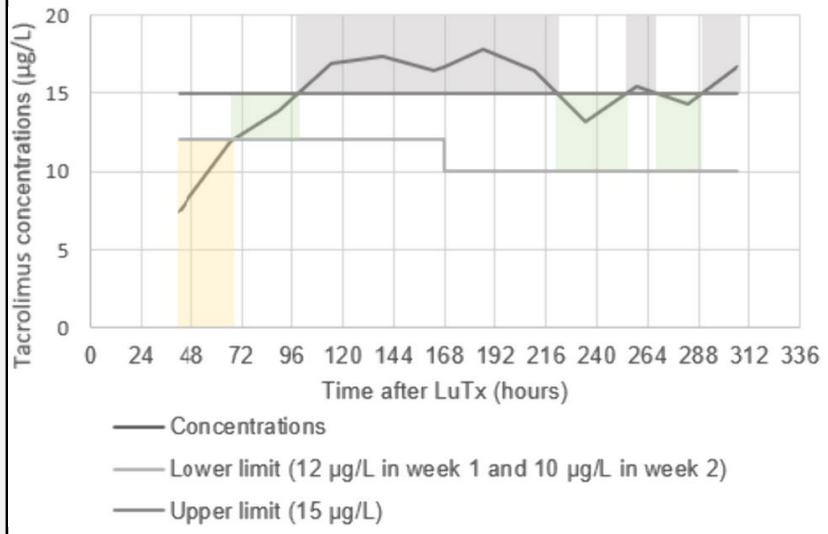

Table 3. Results of secondary outcomes.

Variable/outcome	Oral $n = 224$	Intravenous $n = 298$	*P* value
AKI, *n* (%)	103 (46.0)	127 (42.6)	0.484
AKI stage 1, *n* (%)	55 (24.6)	47 (15.8)	0.014
AKI stage 2, *n* (%)	23 (10.3)	38 (12.8)	0.367
AKI stage 3, *n* (%)	25 (11.2)	42 (14.1)	0.307
RRT in the first 14 days after LuTx, *n* (%)	26 (11.6)	45 (15.1)	0.249
Rejection, *n* (%)	55 (24.6)	53 (17.8)	0.059
Major confounders and effect modifiers for AKI, IPV% and TTR%			
ECLS in the first 14 days after LuTx, *n* (%)	79 (35.3)	60 (20.1)	< 0.001
Lowest Ht in the first 14 days after LuTx (L/L), mean ± SD	0.28 ± 0.07	0.23 ± 0.06	< 0.001

AKI acute kidney injury, *ECLS* extra-corporeal life support, *Ht* hematocrit, *IPV%* percentage of intrapatient variability, *LuTx* lung transplantation, *RRT* renal replacement therapy, *SD* standard deviation, *TTR%* percentage of time within the therapeutic range

Reviewer's Comments

- The study highlights potential advantages of intravenous tacrolimus for reducing variability post-lung transplantation by bypassing the gastrointestinal tract and first-pass metabolism, minimizing patient-specific absorption factors.
- The higher IPV% and lower TTR% in the oral group underline the challenges of maintaining consistent drug levels with oral administration.
- The lack of significant differences in overall AKI and rejection rates between the groups is notable, suggesting that intravenous administration is not associated with increased adverse outcomes.

Limitations

- The study did not collect all concomitant medications, such as azole antifungals, which could impact tacrolimus levels and outcomes due to potential drug-drug interactions.
- The follow-up period beyond the initial 14 days post-transplant was not included, limiting the assessment of long-term variability and its impact on clinical outcomes.
- The study did not include area under the curve (AUC) estimates for tacrolimus exposure, which would have provided a more comprehensive understanding of the PK and potential impact on clinical outcomes.
- The study was retrospective, and while efforts were made to control for confounding factors, prospective studies are needed to confirm these findings.

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Direct oral anticoagulants versus warfarin in adult heart transplant recipients

Shitanishi, et al. *JHLT Open* 2024 | https://doi.org/10.1016/j.jhlto.2024.100061

Study Highlights

Objective: Aimed to look at the incidence of bleeding and breakthrough thrombosis of direct oral anticoagulants (DOAC) vs warfarin in heart transplant (OHT) patients.

Methods: Retrospective, single center, cohort evaluating all OHT patients between 1/2010 – 7/2021.

Results: Ninety-five patients were included with about 86% of patients on concomitant azole antifungals (56% being fluconazole). Mean duration of anticoagulation was 433.7 (±572.7 days). There were 17 total bleeding events; the DOAC group had lower bleeding rates compared to the warfarin group (41% v 58% p=0.0077). 7 were major bleeds and 10 were minor bleeds. There were 6 breakthrough thrombotic events, all in the DOAC group. 4 of the 6 thrombotic events had dosing deviations from package labeling.

Conclusion: DOAC therapy in OHT recipients may be safer than warfarin; however additional research is needed to optimize practice for potential drug interactions and renal dysfunction.

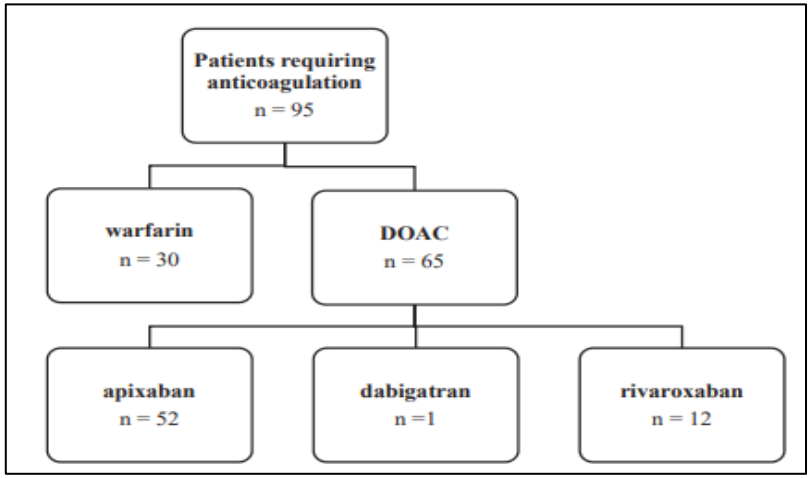
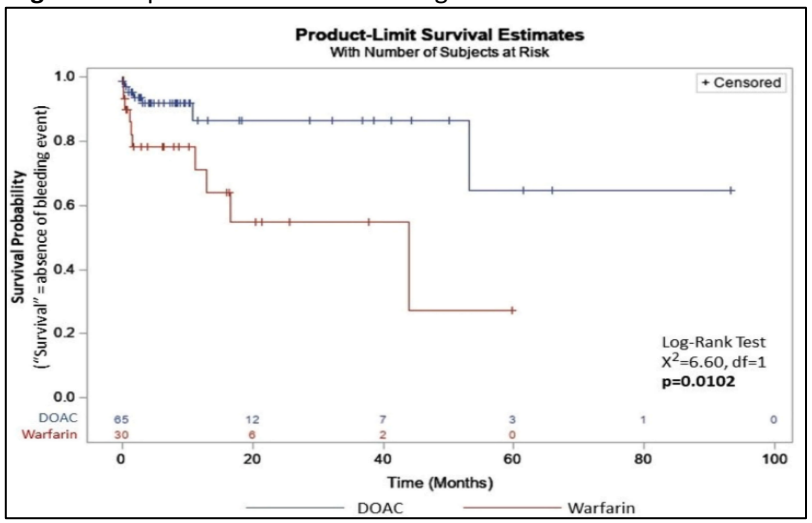


Figure 1: Breakdown of patients on warfarin vs DOAC

Figure 2: Kaplan-Meier curve showing time-to-bleed



Reviewer's Comments

- Long average duration of anticoagulation use.
- Kaplan-Meier curve showing that patients on warfarin had a quicker time to bleed vs DOAC.
- Average time from anticoagulation start to bleeding event happened ~ 9 months into therapy. Average time from transplant to bleed was 2 years 10 months.
- No mention of what the "standard" of practice was regarding holding anticoagulation around routine procedures (endomyocardial biopsy, LHC with IVUS, etc).

Limitations

- Power analysis was not performed, however low incidence of both bleeding and thrombotic events.
- Single center, retrospective, chart
- Lower DOAC bleed rate possibly due to dose reductions?
  - No comparison of patients without either event.
  - Would be beneficial to see how many patients in the DOAC group had dose reductions.

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Results from randomized trial of pirfenidone in patients with chronic rejection (STOP-CLAD study)

Combs, et al. J Heart Lung Transplant 2024 | https://doi.org/10.1016/j.healun.2024.05.013

Study Highlights

Objective: Chronic lung allograft dysfunction (CLAD) remains the leading cause of poor outcomes following lung transplant and is characterized by fibrosis of small airways or pleuroparenchymal fibroelastosis. Pirfenidone, an antifibrotic medication, may be beneficial in patients with CLAD.

Methods: A single-center, placebo-controlled, double-blind randomized trial performed from 5/5/2018-12/3/2019. Lung transplant recipients at least 6 months post-transplant with established baseline lung function of at least 50% predicted values who met ISHLT criteria for CLAD diagnosis were included. Primary outcome was change in lung allograft volume with functional small airways disease (PRM^{fSAD}) over 24 weeks.

Results: Baseline characteristics were similar between groups. There was no difference observed between groups with regards to PRM^{fSAD} and PRM^{PD}. Pirfenidone was not associated with difference in change in FEV_1 over the 24-week period compared to placebo. Gastrointestinal side effects were more common in the pirfenidone group.

Conclusions: Pirfenidone for CLAD was not associated with a significant difference in progression of radiographic allograft dysfunction or in lung function decline.

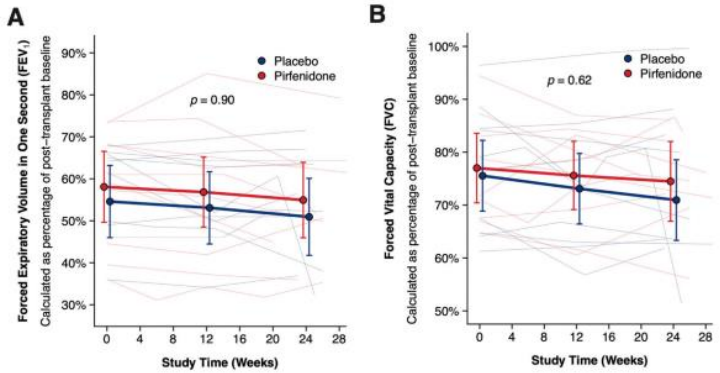

Figure 1. Change in parametric response mapping parameters. **A)** PRM^{fSAD}; **B)** PRM^{PD}

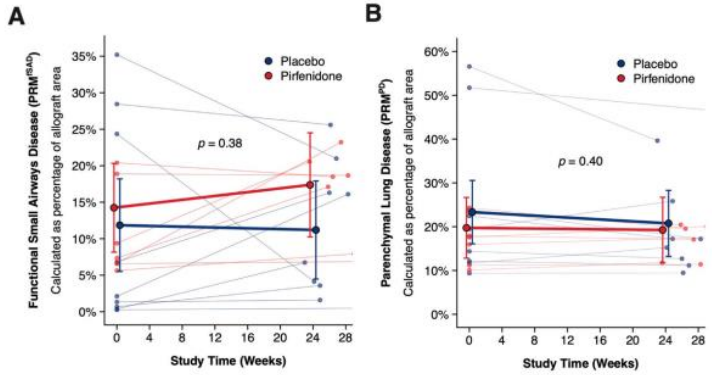

Figure 2. Change in pulmonary function (relative to post-transplant baseline values). **A)** FEV_1; **B)** FVC

Reviewer's Comments

- Pirfenidone has been shown to slow lung function decline in patients with idiopathic pulmonary fibrosis and theoretically may be beneficial in CLAD
- Pirfenidone had no impact on progression of radiographic allograft dysfunction or in lung function decline
- Larger studies are needed to assess impact of pirfenidone on CLAD

Limitations

- Single center study, limiting generalizability
- Enrollment was stopped early due to COVID-19 pandemic, leaving the study underpowered
- Patients were only followed for 24 weeks, which may not be long enough to see full impact
- Exploratory biomarker utilized as primary endpoint and standard assessment of CLAD was only used as secondary endpoint (i.e. FEV_1)
- Data on other CLAD therapies was not included
- Evaluated effect on CLAD generally not based on BOS vs RAS alone – theoretically there may be better impact on RAS patients
- Pre-existing gastrointestinal symptoms and high number of pills may limit clinical utility of pirfenidone in transplant recipients