Safety and tolerability of high intensity statin therapy in heart transplant patients receiving immunosuppression with tacrolimus

Shelby Tjugum, Pharm.D., Stephanie Heeney, Pharm.D., Morgan Corkish, Pharm.D. BCPS, Ian Hollis, Pharm.D. BCPS – AQ Cardiology

Department of Pharmacy, University of North Carolina Health Care, Chapel Hill, NC, United States

BACKGROUND & PURPOSE

- Following heart transplantation (HT), HMG CoA reductase inhibitors (statins) reduce total and low-density lipoprotein (LDL) cholesterol, development of cardiac allograft vasculopathy (CAV), and mortality.[1,2]
- ISHLT guidelines give a Class I recommendation to initiate statin therapy in all HT patients 1-2 weeks post-transplantation, regardless of cholesterol levels.[3]
- Despite the potential benefits of high intensity statin therapy, these guidelines recommend lower doses than those recommended for hyperlipidemia due to a potential pharmacokinetic interaction with calcineurin inhibitors.[3]
- Several studies in HT patients have demonstrated the safety and efficacy of low or moderate intensity statins, however little data exists using high intensity statins in patients receiving tacrolimus.[4-6]
- At the University of North Carolina (UNC) Medical Center, all patients are prescribed a moderate intensity statin at time of HT, but are converted to high intensity statin if they develop hyperlipidemia or CAV.
- **Purpose:** to evaluate the safety and efficacy of high intensity statins when compared to moderate intensity statins in HT recipients on tacrolimus-based immunosuppression.

METHODS

Study Design:
- Retrospective, single center
- Heart transplant recipients Jan 2005 – Dec 2017
- Patients identified from program's comprehensive database
- Outcomes compared 6 months prior to and 6 months post conversion to high intensity statin

Inclusion Criteria:
- Tacrolimus based-regimen
- Converted from moderate → high intensity statin

Exclusion Criteria:
- <18 years old at time of transplant
- Pregnant
- Baseline liver failure or acute liver failure
- Documented statin sensitivity

Primary Endpoint:
- Rate of statin tolerability the first 6 months after conversion to a high intensity statin. Intolerability defined as evidence of myalgia, rhabdomyolysis, or hepatotoxicity, or any statin dose reduction or discontinuation due to adverse drug events

Secondary Endpoint:
- Reduction in total and LDL cholesterol within 6 months of conversion to high intensity statin

RESULTS

Figure 1. Inclusion/Exclusion

153 heart transplants performed during study period

129 patients excluded
91 Never converted to HI statin
17 Age < 18 years old
10 Died during HT admission
9 Documented statin allergy
2 No documentation in EMR

24 patients analyzed

Figure 2. Indication for Statin Conversion

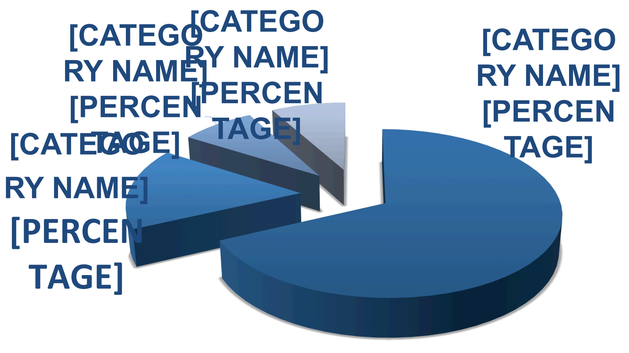

Table 1. Baseline Characteristics

Pre-Transplant (n=24)	
Age at time of HT (y), median [IQR]	50 [43-58]
Male sex, n (%)	19 (79)
Etiology of Heart Failure, n (%)	
Non-Ischemic	15 (63)
Ischemic	9 (37)
Co-Morbid Conditions, n (%)	
Hypertension	11 (46)
Diabetes	6 (25)
Coronary Artery Disease	10 (42)
Peripheral Artery Disease	1 (4)
Prior Statin Therapy, n (%)	
Simvastatin 10 mg	1 (4)
Atorvastatin 10-20 mg	3 (12)
Pravastatin 40-80 mg	1 (4)
Atorvastatin 40-80 mg	7 (29)
Time of High Intensity Statin Conversion (n=24)	
Anti-Proliferative Agents, n (%)	
Mycophenolate mofetil	13 (54)
Azathioprine	3 (12)
mTOR Inhibitors (Sirolimus), n (%)	4 (16)
Steroids, n (%)	6 (24)
Post-High Intensity Statin Conversion (n=24)	
Time to statin conversion (days), median [IQR]	851 [364-1592]
High Intensity Statin Therapy, n (%)	
Atorvastatin 40-80 mg	23 (96)
Rosuvastatin 20-40 mg	1 (4)
Tacrolimus trough (ng/mL), median [IQR]	7.2 [5.0-9.0]
Interacting Medications, n (%)	
Colchicine	2 (8)
Diltiazem	16 (67)
Methimazole	1 (4)
Niacin	1 (4)
Voriconazole	3 (13)

Table 2. Tolerability and Efficacy Data

Primary Endpoint: Safety and Tolerability (n = 24)	Pre-Conversion[a]	Post-Conversion[b]
Myalgia, n (%)	1 (4)	1 (4)
Rhabdomyolysis, n (%)	0	0
Hepatotoxicity, n (%)	0	0
Dose Reduction due to ADE, n (%)	-	0
Discontinuation due to ADE, n (%)	-	0
Composite Tolerability Endpoint	-	1 (4)[c]

Secondary Endpoint: Efficacy (n = 24)	Pre-Conversion[a]	Post-Conversion[b]	Absolute Change (P-value)
Total Cholesterol (mg/dL)	181	146	35 (0.02)
LDL Cholesterol (mg/dL)	100	81	19 (0.10)

[a] 6 months prior to conversion to high intensity statin
[b] 6 months after conversion to high intensity statin
[C] p value: > 0.99

CONCLUSIONS

- High intensity statin therapy appears to be safe and efficacious in HT recipients receiving tacrolimus.
- Atorvastatin 40 – 80 mg per day is a reasonable option for treatment of hyperlipidemia refractory to lower intensity statins.

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DISCLOSURES

Authors of this presentation have the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation:

Shelby Tjugum: Nothing to disclose, Stephanie Heeney: Nothing to disclose, Morgan Corkish: Nothing to disclose, Ian Hollis: Nothing to disclose