Effect of Inhaled Tacrolimus on Ischemia Reperfusion Injury in Rat Lung Transplant Model

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Disclosures

- Robert Williams and Jay Peters: Patent rights for inhaled tacrolimus have been sold to the UT Board of Regents.
- None of the other authors have anything to disclose.
Problems

• Ischemia Reperfusion Injury (IR Injury) is inevitable in transplantation

• Contributes to primary graft dysfunction (PGD)

• Negatively affects overall survival after lung transplantation
Effect of Tacrolimus on IR-Injury

- Cytokines ↑
- Adhesion Molecules ↑

Macrophage activation

IRI Induced Lung Injury

- Pulmonary edema
- Worsening oxygenation & A-a gradient

Neutrophil activation

T-cell activation

PVR & Pvasc ↑
Inhaled nanoparticle Tacrolimus

Standard

Nanoparticle

Diameter: 10,000 nm

Diameter: 200 nm
Pharmacokinetics

Peak lung levels
Peak blood levels


Simmons JD, Johnson SB et al, The Efficacy of Inhaled Nanoparticle Tacrolimus in Preventing Rejection in an Orthotopic Rat Lung Transplant Model, Aust society presentation June 2011
Hypothesis

Administration of inhaled nanoparticle Tacrolimus to the *donor* prior to procurement will attenuate ischemia reperfusion injury after lung transplantation
Orthotopic Rat Lung Transplant
Study design

- **Functional assessment**
  - Arterial Blood Gas

- **Cellular changes**
  - Flow cytometry

- **Cytokines**
  - Luminex Assay

- **Tacrolimus levels**
  - Liquid chromatography/mass spectrometry

**Control Group:** (n=6)
- Inhaled Lactose

**Treatment Group:** (n=6)
- Inhaled Lactose + NP Tacrolimus

Donor pretreatment

- Donor lung harvest
  - 3 hrs ischemia

- Orthotopic left lung transplant
  - 4 hrs reperfusion

Recipient euthanized

Functional assessment

- Celluar changes

- Cytokines

- Tacrolimus levels
Results: Oxygenation

**PO$_2$**

- **Control**
  - PO$_2$ mmHg: 0
  - n = 6

- **Treatment**
  - PO$_2$ mmHg: 600
  - n = 6

* p < 0.01

**PO$_2$ level vs Tacrolimus level**

- Tacrolimus level (pg/mg) range: 700 to 1100
- PO$_2$ level range: 0 to 700

**n = 6**
Results: Neutrophils

Neutrophils

Control

Treatment

n = 6

p = ns

Left Lung CD 11b High + Cells vs Tacrolimus level

Left Lung CD 11b High + Cells (count x10^9/g of lung tissue)

Tacrolimus level (pg/mg)
Results: Cytokines

TNF

IL-6

IL-1b

Control (N = 6)  Treatment (N = 6)

Control (N = 6)  Treatment (N = 6)
Conclusion

Inhaled nanoparticle Tacrolimus treatment of lung donors is associated with attenuation of ischemia-reperfusion injury on a functional level in lung transplantation
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