ORGAN SHARING, DELAYED GRAFT FUNCTION, AND INHALED CARBON MONOXIDE: A BENCH TO BEDSIDE CASE STUDY

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DISCLOSURES

- No Disclosures
- No Recommendations for Off Label Use of CO
The Pathway of Heme Metabolism

*Endogenous Production of CO*

Motterlini, R & Otterbein, L.E. *Nature Reviews*, 2010
Background

**Signaling**


**Intercellular Messenger in CNS**


**Vascular Biology**


**Anti-Inflammatory**

Potential Mechanisms of Action of CO Delivered as a Gas or as a CO-RM
**Modes of CO Delivery**

**CO Gas**
- Inert, non-metabolized, cellular targets well-defined. Inhaled therapy only.
- Specific delivery device required, elevates COHb.
- FDA approved trials.

**CO-RM**
- Small molecule, bioavailable, multiple routes of delivery possible.
- Site-specific delivery with low COHb.
- Backbone molecule presents challenging toxicology.
- Preclinical development

**HBCOC**
- Similar PK/PD as inhaled CO.
- Requires hospital delivery.
- Potential interference as NO scavenger and non-specific PEG effects.
- FDA-approved trials.
CO Provides Protection Against Hyperoxic Lung Injury


CO: 250 ppm continuously
CO Provides Protection Against Hyperoxic Lung Injury

- Dose dependent ↑ survival with CO
- ↓ pleural effusion and protein accumulation in airways
- Histologically devoid of injury or inflammation
- Neutrophil influx into the airways & total lung apoptotic index were strikingly reduced
- CO reversed the ↑ pleural effusion seen in rats treated with SnPP (tin protoporphyrin), an inhibitor of HO-1

CO: 250 ppm continuously

CO Inhibits LPS-Induced Production of TNF-α While Increasing IL-10 Production

Experimental Model of Carotid Artery Injury

1 hr Exposure

Sprague Dawley

Carotid Injury

21 Days

Intimal Hyperplasia

In Vivo

Sprague Dawley Carotid Injury 21 Days

In Vivo

1 hr Exposure

CO 100 ppm

Carotid Injury

Sprague Dawley

21 Days

Intimal Hyperplasia

CO Suppresses Intimal Hyperplasia Associated with Balloon Injury

INO Therapeutics

- Owned by AGA-Linde Healthcare (Germany and Sweden)
- Manufactured and marketed INOMAX (inhaled nitric oxide) that was approved by the FDA in 1999
- Experts in biologic gas delivery and device development
- Aga Linde/iNO Therapeutics (iNOT) performed first Phase I safety and tolerability studies of inhaled CO (iCO) in man (2004)
- AL and iNOT interested in potential clinical applications of CO; meetings with experts (2005)
- Decision to pursue an indication in delayed graft function (DGF) after kidney transplantation based on compelling preclinical data
Delayed Graft Function (DGF) for DCDD vs. Non-DCDDD Kidneys (with and without ECD)

Adjusted Relative Risk (RR) of Graft Failure by DGF and Donor Type

KAS AFTER 18-20 MONTHS: TRENDS*

- Volume of deceased donor kidney transplant increased by 6.9% from the year prior to KAS implementation to 18 months after

- Significant “bolus effects” have occurred for candidates who received additional transplant priority under KAS

- The % of transplant recipients experiencing DGF increased initially post-KAS but has since declined slightly

KAS AFTER 18-20 MONTHS: TRENDS*

- Kidney discard rate after KAS has remained higher than the period prior to KAS - from 18.5% to 19.8% (Especially for KDPT between 86-100)
- Transplants for pediatric patients (0-17) have declined slightly although pediatric patients continue to receive priority & are more often receiving kidneys expected to last longer (lower KDPI)
- Six-month kidney graft survival rate decreased slightly but continues to exceed 95% (patient survival decreased slightly but remains above 97%)

Low-Dose CO Inhalation Prevents Development of Chronic Allograft Nephropathy

Factors Influencing Decision to Study iCO in DGF in Kidney Transplant Recipients

- Scientific data in large animal models suggesting benefit
- Unmet need
- Candidate for fast track and orphan drug status
- Consistent with corporate mission and expertise in providing biologic gases for clinical use
  - Scientific interest in advancing the field of basic and clinical investigation and patient care
  - Unique drug-device combination expertise; strong IP
  - Profitable business model
Factors Influencing Decision to Avoid the Study of iCO in Deceased Donors

• Exposure of all organs (even though perceived benefit for all i.e. low risk)
• Logistics for training as well as availability and distribution of cylinders and devices
• Organs distributed to multiple patients at multiple sites with little advance notice of physicians and patients
  • How to obtain IRB approval and consent
  • Consent concerns in DCDD (who? ethics?)
• Potential to affect outcomes
Bench to Bedside: Covox™

• FDA: Pre-IND Meeting (2006)
• Drug-Device Development of Covox™ (2006)
  • For use pre-op (donor), intra op (donor or recipient), or post op (recipient) mg/kg/hr
• Clinical Trial Design (C201 2006)
  • Kidney transplant recipients (intraop or post-op)
  • No donor treatment
CO Delivery Device

CO Prescription
mg/kg/hr

3 mg/kg/hr ~ 250 ppm

Dose Setting Controls
1. Dose (mg)
2. Ideal body weight (kg)
3. Time (hrs)
CO Delivery Device

CO Prescription
mg/kg/hr

3 mg/kg/hr ~ 250 ppm

Dose Setting Controls
1. Dose (mg)
2. Ideal body weight (kg)
3. Time (hrs)
Pharmacokinetics of Covox

(2 mg/kg/hr; 60 min exposure)
Developed Kidney DGF Model In Swine

- Development of laboratory model of DGF that mimicked the clinical entity
- Testing of hypothesis and elucidation of possible mechanisms
- Recipient treatment only
- No funding for donor treatment even though of scientific interest
- Funded by INO Therapeutics
Delayed Graft Function Model In Pig
WIT + CIT

Pig Kidney Allograft

Kidney (nephrectomized)
Ureter
Bladder

Recipient Pig

Transplanted Kidney

CO to Recipient only

Warm Ischemia
+ Cold Ischemia

Kidney Transplant
Kidney Function

sCr/BUN daily
Intraoperative CO Reduces Delayed Graft Function

CO 3 mg/kg Intraoperatively for 1 hour

Hanto DW, et al. AJT 2010; 10:2421-2430
C201 Clinical Trial Initiated 2007

- Preliminary Cr and GFR data demonstrated dose-dependent trend toward improved renal function in intraoperative cohort (31 of 32 planned patients entered into trial)
Bench to Bedside: Covox™

- FDA
- IND and Fast Track approval (2007)
- Orphan drug designation (2008)
Demise of the Project

- INO Therapeutics purchased by Ikaria (2007)
- Requested higher dose of Covox™ (2008)
- FDA placed a clinical hold and requested additional testing (2008). Requested detailed cardiac monitoring and additional MRI post-op.
- Clinical hold released (2009)
- Ikaria decides not to pursue further clinical studies (2010)
- Ikaria now owned by Mallinckrodt Pharmaceuticals (2015)
- Multiple groups pursuing CO therapeutics
Ethics Guidelines for Research with the Recently Dead

Consensus Panel on Research with the Recently Dead (CPRRD)

- Must respect value and dignity of the once-living person; honoring preferences
- Multidisciplinary scientific review & approval should be required
  - Assess validity and value; preclinical studies
  - Address significant question(s) & use methods likely to produce valid results
  - When research involves drugs approval by government agencies (e.g. FDA) or prior animal toxicology studies are not necessary, but results must be potentially translatable to living humans
- Invasiveness and negative consequences (family) should be avoided
- Recommend community involvement in review, approval and oversight (relevant community = potential research subjects and others including 1/4 lay membership as recommended by National Bioethics Advisory Commission)
Ethics Guidelines for Research with the Recently Dead

Consensus Panel on Research with the Recently Dead (CPRRD)

• Investigators must justify having chosen this subject population
  • Rejects the requirement that research with the deceased be a last resort

• Organ procurement, because of its potential to benefit current individuals, takes ethical priority over research

• Death determination by physicians not involved in the research study

• Procedures must be respectful but do not need to be identical to those used with the living

• Duration of the study should be limited to one day unless valid scientific reasons for a longer period
Ethics Guidelines for Research with the Recently Dead

Consensus Panel on Research with the Recently Dead (CPRRD)

- Obtain consent from competent prospective subjects or their legally authorized representatives
- Healthcare worker participation in research protocols should be voluntary
- Confidentiality must be maintained
- The research protocol should address how the research will be funded; no cost or burden on subject’s estate, family or surrogates; payment or incentives for participation should not be offered
- Explain the ultimate disposition of the body and whether it can be viewed after the research is completed
- Consider offering results to next of kin
“Standard of Care Interventions” (low risk) vs. “Experimental Interventions” (low, mod, high risk)

- Brain dead donors
  - Viewed the same in either scenario according to the CPRRD (hypothermia, CO, etc.)
- Donors after circulatory determination (DCDD) of death
  - Important study population because of poor organ function post donation
  - Would presumably fall under federal regulations protecting living human subjects
- Transplant recipients
  - Are recipients experimental subjects when “standard of care interventions” or “experimental interventions” (e.g. drugs under IND) are studied?
  - Does the degree of risk inform the decision?
  - Does the need for recipient information inform the decision?
  - How does one obtain consent from recipients when organs may be allocated to any of over 200 transplant centers around the country?
“Standard of Care Interventions” (low risk) vs. “Experimental Interventions” (low, mod, high risk)

- Organ Allocation Issues
  - How does one obtain consent from recipients when organs may be allocated to any of over 200 transplant centers and thousands of potential recipients across the country?
    - National IRB reviews and approves donor intervention studies
    - National IRB accepted by institutional IRB (active involvement or oversight of national IRB)
    - Consent obtained on listing?
  - Are allocation policies violated if waitlisted recipients who do not consent to the study are then passed over when an on study organ that would have been allocated to them off study goes to another recipient further down on the list? Is fairness violated? Will this then lead to coercion of recipients to consent?
End