AST | AMERICAN SOCIETY OF TRANSPLANTATION

# To Treat or Not To Treat What Induction Therapy is Beneficial?

David P. Nelson, MD, F.A.S.T.
Chief, Heart Transplant Medicine
INTEGRIS Baptist Medical Center

CEOT CUTTING EDGE of TRANSPLANTATION

**TRANSPLANT SUMMIT** 2019

***NO SIZE FITS ALL:*** *Uncovering the Potential of Personalized Transplantation*

FEBRUARY 21–23, 2019 • ARIZONA BILTMORE • PHOENIX, AZ

## Disclosure

I HAVE NO RELEVANT PERSONAL FINANCIAL RELATIONSHIPS.

## Learning Objectives

1. Summarize literature of IL2a and RATG against controls and each other

2. Recommend
   A) Indications
   B) Methods for safer use
   C) Monitoring induction use

CD3 Monitoring

- Also called “intermittent” instead of “uniform” dosing
- Substantially decreases cost, sometimes decreases infection, decreases heme toxicity
- Targets of <20-25, 50-100 and <100 cells/uL reported. ALC <200 cells/uL reported to be non flow-cyto surrogate
- Studies found successful efficacy with induction, CNI delay, and treating rejection including steroid resistant
- Renal studies better than thoracic – include randomized and larger

## CD3 References


Abouna G et al. (Kidney) Transplantation 1995; 11:1564

Buchler M et al. (Kidney) Transplant Proc. 1996; 5:2817

Gorrie M et al. (Kidney) Clin Lab Haem. 1997; 19:53

Djamali A et al. (Kidney) Transplantation 2000; 69:799

Peddi VR et al. (Kidney) Transplantation 2002; 73:1514

Krasinskas AM et al. (Thoracic) Transplantation 2002; 73:1339

Uber WE et al. (Heart) Transpl Proc 2004; 36:3245

Furlanetto G et al. (Kidney) J Bras Nephrol 2017; 39:181

# Induction indications

- Rejection Risk
- CNI sparing for renal recovery
- CNI elimination: SCHEDULE
- RATG decreases CAV
- RATG may increase 5-10 year graft survival
- Decrease PGD

Beniaminovitz A et al. NEJM 2000; 342: 613
Columbia

- Randomized Hearts
- 28 daclizumab  27 control
- ACR ≥ grade 2 x 3 months
  mean frequency per patient
  0.64 control  0.19 IL2a
  63% control  18% IL2a
- Infections no significant difference
- 5 control got cytolytics for HD significant rejection

## IL2 ANTAGONISTS

Meta analysis renal randomized trials
Webster A et al. Transplantation 2004; 77:166

- 117 reports, 38 trials, 4893 patients
- versus placebo 17 trials =
  A. Graft loss no different at 1 year (14 trials) or 3 year (4 trials)
  B. Acute rejection 34% less
     at 6 months (12 trials RR 0.66)
     at 12 months (10 trials RR 0.67)
  C. 49% reduction in steroid resistant rejection at 6 months (7 trials RR 0.51)
  D. No difference CMV or CA
- only 7 trials used FK
- 14 trials versus mono or polyclonal Ab showed comparable rejection but more adverse effects with Abs
- No difference between daclizumab and basiliximab

Mehra M et al. JHLTX 2005; 24:1297

- Heart
- Multicenter, randomized, double blind
- Pharmakinetcs not efficacy study
- 25 IL2, 31 placebo
- Basiliximab exceeded CD25 saturation Threshold AV 38 ± 13 days (0.2ug/ml)
- No difference ACR, HD compromise, death, adverse events, infections x6 months

Hershberger RE et al. NEJM 2005; 352:2749

- Multicenter/placebo/randomized
- 434 Hearts/daclizumab
- Primary endpoint composite:
  Moderate-severe rejection, graft dysfunction, death or graft loss in first 6 months

| | Primary | Rejection Rate |
|---|---|---|
| Daclizumab | 35% | 25% |
| Placebo | 47% | 41% |

Death from infection:
6 daclizumab died
0 placebo died
All 6 also received cytolytic Rx

Grundy N et al. JHLTX 2009; 28:1279

- Pediatric heart
- Basiliximab intra-op 59
  post-op 33
  none 29
- Freedom from ≥ 3A ACR at 1 year
  intra-op 95%
  post-op 70%
  none 72%
- CD25 <0.2% POD 1 + 10
  In both IL2 groups e.g. –
  No washout
- Infection rate unchanged
- Manufacturer, FDA and British National Formulary recommend pre-op Basiliximab

ATG (Equine/Rabbit)

- German/Austrian/Swiss expert consensus
  Zuckermann, A et al. Tx Int. ESOT 2014; 28:259

  a) well referenced regarding renal protection, steroid sparing, rejection risk
  b) Cautioned balancing potential benefit against infection risk in VADs

- Use focuses on rejection risk or CNI sparing for nephroprotection

- ISHLT Guidelines Costanzo MR et al. JHLTX 2010; 29:214 recommended above

- Consensus Conference recommended RATG in AMR-at risk and desensitized patients. Kobashigawa J, Mehra M, West L et al. JHLTX 2009; 28:213

Whitson BA et al. (Higgins). Clin Tx 2015; 29:9

- UNOS 2001-2011 excluded OKT3
- of induced 55% IL2a, 40% ALG/ATG/RATG, 4% alemtuzumab
- Multivariable and propensity models used
- No survival advantage with induction

COCHRANE LIBRARY
INDUCTION HEART

- IL2a/ATG vs each other or controls
- 1946-2012; 22-RCTs
- No differences in mortality, infection, CMV, PTLD, CA, adverse events, CAV, others
- Acute Rejection significantly less ILS2a vs control  33% vs 45%
- AR stat. IL2a > ATG  27% vs 11%
- Trials had high bias risk, more RCTs needed

Penninga L, et al. Cochrane Database of Systematic Reviews 2013; 12 Art. No: CD008842

SUCCESSFUL INDUCTION WITH DELAYED CNI HEART

- delay ranges from 3 to 18 days
- used for both pre and post-op renal dysfunction

Delgado, DH et al. JHLTX 2005; 24:166 - IL2a
Rosenberg, PR et al. JHLTX 2005; 24:1327 - RATG
Cantarovich, M et al. Transplantation. 2004; 78:779 - RATG
Aliabdi AZ, et al. JHLTX 2016; 35:517 - RATG

- CNI delay with PRA >70% undetermined
  Ruan V et al. (Kobashigawa) Review. Tx Proc 2016; 49:253

RATG with delayed CNI
Cantarovich ibid

- 15 with Cr ≥ 150uM got RATG every 2-5 days to keep ALC <200;
  controls RATG 1.5 ml/Kg/day x5.
- CyA delayed in study group for 12 ± 8 days until Cr < 150uM
- Cumulative RATG dose: study 6 vs control 7 mg/Kg
- 1 year survival and rejection rates without statistically significant difference
- Trend toward lower rejection in study group (27% vs 59%)
  a) uremia protective?
  b) ATG induced apoptosis of activated lymphocytes is IL2 dependent and prevented by CyA, FK, SRL
  Genastier, L et al. Blood 1998; 91:2360
  c) My question: is duration of exposure better than compressed speed of dosing

# RATG with reduced CNI

Andreassen AK et al. SCHEDULE Study. AJT 2014; 14:1828

- Both groups get steroids, MMF and ATG “up to 5 days”
- Study group: everolimus 3-6 mg/ml
  CyA 75-175 ng/ml
  until week 7, then
  EVR 6-10 ng/ml and d/c CyA
- Control CyA 150-350 x 2 months, tapered to 60-200 at 6 months
- 1 year GFR EVR 79.8 vs CyA 61.5
- CAV by IVUS and CMV less in EVR
- ≥ grade 2 ACR 40% EVR, 18% CyA
- no AMR or HD ACR in either group
- all ACR steroid responsive
- survival, PRA, DSA unreported

# Induction in Rejection Risk

Higgins, R et al. JHLTX 2005; 24:392

- CTRD 1990-2001; 6,553 patients
- Induction = survival advantage if 1 year rejection death risk >5%
- Induction = survival disadvantage if 1 year rejection death risk <2%
- Induction: none 66%, OKT3 19%, ATG 7%, RATG 1.2%
- Beneficiaries were

  ≥ 4 HLA mismatch and either

  a) < 25 year-old black, or

  b) VAD >6 months

  i. nonblack <30 years old

  ii. Black <35 years old
- One important variable different between groups: Cr>2.0 at Transplant

  4.2% non-induction, 9.3% induction

## RATG for Presensitized

- Recommended by 2009 Consensus Conference

  Eckman PM et al. Curr Opin. Organ Transplant 2010; 15:650

- Lower incidence de novo DSA in moderately sensitized renal transplant.

  Brokhof, MM et al. Transplantation. 2014; 97:612

## RATG for Non-sensitized

- lower denovo antibodies 11% vs 29% but no difference in donor-specific denovo 9% vs 12%

  Rafie M et al. Tx Proc. 2014; 46:3570

## Steroid Free with RATG

- 2 studies Renal. ES Woodle et al.
  D/C steroids 7 days/early
  Ann Surg 2008; 248:564 and Living Donors Clin Tx 2010; 24:73

- Heart 32 low risk randomized to RATG no steroid vs induction-free with steroids.
  All got FK target 15-20ng/ml x 3 months. ACR similar.
  Yamani MH et al. Clin Tx 2008; 22:76

- Data on RATG associated steroid elimination “too sketchy”
  Zuckermann, A et al. ESOT 2014; 28:259

# RATG Decreases CAV: IVUS

Azarbal B et al. Clin Heart Fail. 2016; 9:e00-2252

- RATG indication (Cedars) was delay CNI or sensitization
- 46 of 103 (44.7%) got RATG Av 3.9 ± 1.2 doses
- sensitization = ≥25% PRA
- RATG patients more sensitized 54% vs 14%

# RATG/CAV Azarbal Results

- Reduced 1 year plaque
  Progression max intimal area 1.0 ± 1.2 vs 2.3 ± 2.6mm$^2$
- Max % stenosis 6.3 ± 7.9 vs 12.8 ± 12.3
- Max intimal thickness 0.2 ± 0.2 vs 0.3 ± 0.3mm
- Plaque volume 0.5 ± vs 1.0 ± 1.3mm$^3$/mm
- Rapid plaque progression by max % stenosis (≥ 20%) less in RATG: 4.3% vs 2.63%
- Survival and treated rejection not statistically different

More RATG/CAV Azarbal Results

- First year infection RATG 50% vs 31.6%
- First year DSA RATG 33% vs 7.1%
- First year de novo DSA RATG 20% vs 5.4%

Other References: RATG Decreases CAV by angio


- Zhang R et al. JHLTX 2008; 27:603
- Bonaros N et al. JHLTX 2006; 25:1154
- Zuckerman A et al. JHLTX 2001; 20:196
- Aliabadi A et al. JHLTX 2016; 35:517

## Delayed Graft Function/RATG

Goggins WC et al. Transplantation 2003; 76:798

- 58 cadaveric kidney randomized
- Study group got first RATG dose intra-op; both got same number of doses 4.6 vs 4.8 doses
- DGF study 14.8% control 35.5%
- 16 paired kidneys 12.5% vs 43.8%
- ACR 3.6% vs 16%
- AMR 0 vs 9.7%
- CMV at 6 months 3.7% vs 6.5%
- Speculate with refs Abs to adhesion molecules decrease ischemia – reperfusion injury

## RATG protected heart transplants from ischemic reperfusion

Zarrini P et al. J. Am Coll Cardiol 2016; 67:1452

# RATG vs IL2a

Brennan D at al. NEJM 2006; 355:1967

- Prospective randomized, international, 28 centers
- 141 RATG vs 137 Basiliximab
- High risk DGF or Acute Rejection:
  PRA > 20%, donor Cr 2.5, ischemic time, donor age, race, ≥1 HLA mismatch
- RATG 5 doses vs IL2a 2 doses
- 1 year acute rejection RATG 15% vs 25%
  treated rejection RATG 1.4% vs 8%
- Graft loss and DGF similar
- Infection RATG 85.8% vs 75%
  CMV disease RATG 7.8% vs 17.5%
- Postop DSA unreported; discrimination between ACR and AMR unreported

Brennan RATG vs IL2a ibid

- Author speculates DGF same between groups because IL2a can possibly decrease DGF and cite a review article:
  Sandrinis, Clin Tx 2005; 19:705

- Both RATG and IL2a first doses given intra-op in NEJM study

## ATG vs IL2a

Ansari D et al. J AM Heart Assoc 2016; 5:e002790

- UNOS data, pediatrics, 2001-2013
- 1 year survival comparable
- 5 year survival RATG 76% vs 68%
- 10 year survival RATG 65% vs 49%
- Higher death rate IL2a attributable to graft failure

ATG vs IL2a

Butts R  et al. Pediatric Transplantation. 2018; 22:e13190

- ISHLT data, pediatrics 2000-2015
- ATG more congenital, higher PRA, longer ischemic
- 1 year conditional graft survival
  10 year ATG 71% vs 58%
- CAV ATG 9.9% vs 15.8%
- Death from CAV ATG 28% vs 34%
- Death from graft failure ATG 1.6% vs 10.8%

# INDUCTION LITERATURE CONCLUSIONS

- Long term outcomes confounded by historical AZA/CyA and larger cumulative RATG dosing
- Induction historically  unsophisticated regarding DSA and AMR
- Randomized prospective studies limited
- Recent publications show better 5-10 year survival with RATG over IL2a
- RATG immunosuppression >IL2a: less rejection, infection more with RATG (control or IL2a) unless rejection risk then less
- RATG more demonstrated to safely CNI delay
- RATG more demonstrated to decrease PGD and CAV
- intra-op induction and CD3 monitoring underappreciated

# RECOMMENDATIONS

- Consider using IL2a in everyone not getting RATG, safe and less rejection
- Follow status quo for RATG: use for CNI delay or rejection risk (or SCHEDULE CNI d/c?)
- Consider intra-op RATG or IL2a to
  a) decrease PGD
  b) increase efficacy without increasing immunosuppression
- When converting IL2a to RATG
  a) d/c 2nd IL2a dose
  b) consider decreasing RATG dose and use CD3 monitoring

Mitigate RATG infection risk:

a) Defer or decrease dose or substitute IL2a for ALC<200 or ANC ≤1500
b) peri-op IgG level, give 250ml/kg for IgG ≤400-600
c) don’t exceed cumulative dose of 6.5 mg/kg
d) consider CD3 monitoring
e) cautious use with VAD patient

DOSING

- Cumulative dose 6mg/kg equal efficacy to larger doses in renal transplant

  Agha et al. Transplantation 2002; 28:120

- Review of studies 1999-2009: highest PTLD rate in hearts with does ≥7.5mg/kg

  Marks WH et al. Tx Proc 2011; 43:1345

- Current common practice 1-3.5mg/kg cumulative

  Zuckermann A et al. ESOT 2014; 28:259

RATG DOSE

Rejection Risk:

a) 0.75-1.5mg/kg/day

CNI Delay:

a) 1mg/kg/day with intermittent dosing to keep CD3 <100 cells/uL until renal recovery adequate
b) Don't exceed 6.5 mg/kg cumulative dose if giving in 7 day period
c) Possibly safe and efficacious, to spread RATG doses over 2-6 weeks keeping CD3 <100 cells/uL
   – limited studies; cumulative dose limits undefined