Transfusion Related Immune Modulation (TRIM) safety issues

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Does TRIM exist?
Pre-clinical studies

Anti-inflammatory

↑ Tregs
↓ T cell cytokines
↓ NK cell function
↓ TNF-α, ↑ TGF-β
• Aged or non-LR RBCs promote tumors in mice

Pro-inflammatory

• Neutrophil priming
↑ Pro-inflammatory cytokines

Muszynski et al., Transfusion in press
Does TRIM exist?
Clinical studies

Anti-inflammatory

- ↑ IL-10
- ↓ IL-12, IL-23, TNF-α
- ↓ NK cell function
- ↓ Monocyte function

Pro-inflammatory

- ↑ Pro-inflammatory cytokines
- ↑ CRP, BPI
  - Leukocytosis

Muszynski et al., Transfusion in press
ABLE and RECESS

ABLE

- RCT 1430 ICU patients
- Mean 6 vs. 22 day-old RBCs
- Mean 4.3 units
- No difference in primary outcome (mortality) or secondary outcomes

RECESS

- RCT 1098 complex CT surgery patients
- Mean 7 vs. 28 day-old RBCs
- Median 3 units
- No difference in primary outcome (Δ MODS) or secondary outcomes

Lacroix et al., NEJM 2015
Steiner et al., NEJM 2015
Ancillary studies

ABLE
- 51 standard
- 49 fresh
- Female 51 vs. 49%
- Apache 21.8 vs. 22.9

RECESS
- 28 standard
- 35 fresh
- 27 non-Tx
- 50 healthy controls
- Female 36 vs. 57%
- Hgb 12.9 vs. 11.6 (p<0.01)
- Median 3 vs. 4 units RBCs
Ancillary studies

<table>
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<tr>
<th>ABLE</th>
<th>RECESS</th>
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<tr>
<td>• Cellular immune function</td>
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<td>• EV content and phenotype</td>
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<td>• Cytokine profile</td>
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ABLE: Cytokines

- **Pro-inflammatory**
  - IL-2
  - IL-7
  - IL-12p70
  - IL-17A
  - IL-23
  - IL-21
  - IL-1β
  - IFN-γ
  - TNF-α
  - IFN-γ
  - IL-6

- **T cell function**
  - IL-2
  - IL-7
  - IL-12p70
  - IL-17A
  - IL-23
  - IL-21
  - IL-1β
  - IFN-γ
  - TNF-α
  - IFN-γ
  - IL-6

- **Barrier function**

- **Inflammatory markers**
  - sVCAM-1
  - sICAM-1
  - PAI-1
  - MPO
  - Cystatin C
  - β2-microglobulin
ABLE: Cytokines

Anti-inflammatory Growth factor

Chemokines

Days
pg/mL

IL-10, GM-CSF, EGF, FGF-2, VEGF, PDGF-AB/BB

CXCL11 (I-TAC), RANTES, IP-10, MIP-1β, MIP-1α, IL-8
ABLE: T cell function
ABLE: RBC and platelet-EVS

**Graphs:**
- **RBC EVs:**
  - EVs/µL vs Days
  - CD235a (Glycophorin A)
  - CD108 (Semaphorin 7A)
  - CD41a (GPIIb)
  - CD62P (P-selectin)
- **Platelet EVs:**
  - EVs/µL vs Days
  - Total EVs
  - Annexin-V+

**Days:**
- 0, 10, 20, 30
ABLE: WBC-EVs

**Lymphocyte MPs**

**Monocyte-myeloid EVs**

**Adhesion and co-stim EVs**
Is the fluctuation in EVs due to transfusion or just reflective of the underlying critical illness?
RECESS: transfused vs. non-transfused Lymphocytes

CD15

CD3

CD62L

CD19
RECESS: transfused vs. non-transfused RBCs

Total EVs

CD235a

CD108
RECESS: transfused vs. non-transfused Platelets

CD41a

CD62P
RECESS: transfused vs. non-transfused Cytokines

- IL-23
- RANTES
Conclusions

- TRIM observed variably in the literature

- Some pro- and anti-inflammatory cytokines fall after transfusion in ABLE subjects
  IL-6, IL-8, IL-10, MPO, PAI-1

- Treg level and T cell functions largely unchanged after transfusion in ABLE subjects

- RBC, platelet, and lymphocyte-EVs fall after transfusion in ABLE subjects
Conclusions

• Cytokine modulation variable after transfusion in RECESS subjects

• RECESS subjects recapitulate post-transfusion drop in platelet and lymphocyte-EVs

• RBC-EV levels did not change post-transfusion in RECESS subjects

• Platelet-EV modulation occurred in transfused but not non-transfused subjects

• Need to perform immune monitoring of subjects randomized to transfusion or not to definitively define TRIM
Acknowledgments

BSRI/UCSF
- Heather Inglis
- Ali Danesh
- Sheila Keating
- Mars Stone
- Avani Shah
- Dale Hirschkorn
- John Heitman

ABLE
- Jacque Lacroix
- Irene Watpool

Washington University, St. Louis
- Philip Spinella
- Kenneth Schechtman
- Avril Adelman

NERI
- Susan Assmann
- Julie Miller
- Felicia Trachtenberg

RECESS
- Marie Steiner
- Pampee Young

Funding: DoD, NHLBI