Clinical validity and potential utility of a novel blood-based molecular biomarker for sub-clinical kidney transplant rejection

Findings from the Clinic Trials in Organ Transplant (CTOT 08) Trial


Abstract #250390
Disclosures

Transplant Genomics, Inc. – Equity and Consulting
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Shire – Grant support
One Lambda – speaker

My presentation does include discussion of off-label or investigational use of biomarkers.
Background

- **Hypothesis** - Early graft inflammation leads to worse 24-month transplant outcomes. Molecular biomarkers would allow for early non-invasive detection and would show correlation with worse graft outcome.

- Post-transplant monitoring has not changed in over 2 decades.

- Monitoring with **surveillance biopsies** is the only currently available modality to rule out *sub-clinical* acute rejection (subAR)
  - Invasive
  - Prone to sampling error
  - Variable histologic interpretation
  - Very frequently negative (unnecessary risk)

- **SubAR** is linked to worse outcomes
  - Therefore early detection and treatment may improve graft outcomes.

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CTOT 08 Trial
24-month Multi-Center Observational Study – 5 Centers
Surveillance Biopsies at 2-6, 12 and 24 months

**SubAR**: histology on a surveillance biopsy
- acute rejection (≥ Banff borderline cellular rejection and/or antibody mediated rejection)
- **AND** stable renal function,
  - serum creatinine <2.3 mg/dl and <20% increase in creatinine compared to a minimum of 2-3 prior values over a mean period and range of 132 and 75-187 days, respectively

**Transplant eXcellence (TX)**: normal histology on surveillance biopsy
- (no evidence of rejection - Banff i=0 and t=0, g=0, ptc=0; ci=0 or 1 and ct=0 or 1)
- **AND** stable renal function as defined above. Surveillance biopsies were performed on all subjects at 2-6, 12 and 24 months following transplantation.
Biomarker Discovery

530 CTOT08 Samples Gene Expression (GE) Data

- subAR
- ComBat: Batch 1 vs Batch
- TX

Gene Expression Profile (GEP): 57 Genes (61 probe sets) from RF Model
- 7 genes linked to top 10 IPA immune/inflammatory pathways

ComBat Adjustment By Phenotype

Log2(Expression Distribution)

530 and 138 blood samples all paired with centrally read biopsies were used for discovery and validation respectively.
### Test Performance by Locked Threshold Probability (subAR positive test)

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Paired samples</th>
<th>TX:subAR (% subAR prevalence)</th>
<th>Prob. Thresh</th>
<th>% Neg (Spared biopsy)</th>
<th>NPV</th>
<th>True Neg</th>
<th>False Neg</th>
<th>% Pos (pick up subAR)</th>
<th>PPV</th>
<th>True Pos</th>
<th>False Pos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery set</td>
<td>N=530</td>
<td>400:130 (24.5%)</td>
<td>0.375</td>
<td>74.7%</td>
<td>88%</td>
<td>349</td>
<td>47</td>
<td>25.3%</td>
<td>61%</td>
<td>83</td>
<td>51</td>
</tr>
<tr>
<td>Validation set #1</td>
<td>N=138</td>
<td>96:42 (30.4%)</td>
<td>0.375</td>
<td>71.7%</td>
<td>78%</td>
<td>77</td>
<td>22</td>
<td>28.3%</td>
<td>51%</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Validation set #2</td>
<td>N=129/138</td>
<td>93:36 (27.9%)</td>
<td>0.375</td>
<td>72.1%</td>
<td>80%</td>
<td>74</td>
<td>19</td>
<td>27.9%</td>
<td>47%</td>
<td>17</td>
<td>19</td>
</tr>
</tbody>
</table>

72-75% of patients would have a negative test and could therefore be spared a surveillance biopsy by ruling out the presence of subAR with 78-88% NPV.

The remaining 25-28% would have a positive test and would therefore be at higher risk harboring subAR with 47-61% PPV.
Clinical Endpoints in CTOT 08

- Clinical Composite Endpoint (CCE):
  - 24-month biopsy (central read) with chronic injury – Interstitial Fibrosis/Tubular Atrophy (IFTA) (Banff ≥ Grade II IFTA [ci ≥ 2 or ct ≥ 2]); OR
  - Biopsy-proven acute rejection (BPAR) on any ‘for-cause biopsy’ (central read); OR
  - A decrease in estimated glomerular filtration rate (ΔeGFR) by >10ml/min/1.73m² (CKD-EPI) between 4 - 24 months post-transplant

- De novo DSA: Class I and/or II (local determination)
Clinical Validity – Clinical Phenotype

Based on biopsy results only

Association of Clinical Phenotypes with 24 month Clinical Endpoints

Association between dnDSA with Clinical Phenotype within 1 year Post Transplant

Association of Clinical Phenotypes with dnDSA anytime Post Transplant
Clinical Validity - Gene Expression Profile
Based on GEP Biomarker Results only

**Panel 1**
Association of GEP with dnDSA anytime Post Transplant

- CCE
- IFTA ≥II
- BPAR
- ΔeGFR

**Panel 2**
Association between dnDSA and GEP within 1 year

- Tx only (n=134)
- ≥1 subAR (n=116)
- subAR only (n=34)
SubAR Treatment Follow up - Clinical Utility

<50% of 8-week follow up biopsies after subAR treatment show histological improvement!!

Also detailed in ATC Abstract #250672
Conclusions

• A blood-based biomarker could be used to non-invasively monitor *stable* kidney transplant recipients
  – significantly reducing the need for invasive surveillance biopsies (in 70-75% of patients with negative test with a 78-88% NPV)
  – and to monitor the effectiveness of treatment for subAR, providing informed management of immunosuppression and ultimately better KT outcomes.

• Independent of the biopsy-driven clinical phenotype, the GEP biomarker alone associates with the clinical composite endpoint and *de novo* DSA
Future Directions

• Planned randomized controlled trial to further assess clinical utility
• Biomarker-informed patient management vs. protocol biopsy-informed patient management with assessment of safety and clinical outcomes
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The promise of precision medicine will only be achieved when molecular diagnostics detect actionable differences operating in individual patients, that can inform management and change clinical outcomes.  

Daniel R. Salomon 1953-2016
Thank You