USHERING A NEW ERA OF IMMUNOSUPPRESSION

Flavio Vincenti

Why we need a new paradigm in immunosuppression

- Reduced acute rejection rates have not translated into better long-term graft survival

- Collaborative Transplant Study Results 1998-2007
- CTS Database N=51,303 recipients of deceased donor organs
  - Opelz G, Döhler B. Transplantation 2009;87: 795–802

Causes of death and graft loss after kidney transplantation

- Current regimens do not address causes of graft loss

USRDS adult, 1st kidney-only transplants, 1995–2003, who died with functioning graft (n=10,648)
A NEW PARADIGM IN IMMUNOSUPPRESSION IS NEEDED TO PRESERVE RENAL FUNCTION, DECREASE CARDIOVASCULAR TOXICITIES AND IMPROVE LONG TERM OUTCOME

Profile of Desirable New Agents
- Suppresses T and B cells
- Lacks nephrotoxicity
- Does not aggravate cardiovascular risk factors
- Does not affect glucose metabolism
- Improves compliance

Prototype of Novel Drugs That Represent A Paradigm Shift in Immunosuppressive Regimens
- Costimulation blockade with Belatacept
- JAK3 inhibition with Tasocitinib

A Paradigm Shift in Biologic Immunosuppression
- Biologics for maintenance therapy: required profile
  - No acute toxicities associated with administration
  - Can be delivered in a peripheral vein or subcutaneously
  - Lack immunogenicity
  - Modulation preferable to depletion
**T-Cells Require Costimulation for Full Activation**

CD80/86-CD28 is the most important costimulatory pathway.

- **Signal 1**: Antigen triggers T-cell receptor
- **Signal 2**: Costimulation between ligands

**Activated T-cell**

- Cytokine production
- T-cell proliferation

*Other costimulatory pathways exist that also serve this role*

**APC** = antigen-presenting cell

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**TCR signal only = no activation**

- No cytokine production
- No cell division
- Becomes anergic
- Undergoes apoptosis

**Signal 1 only**

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**CTLA4 Negatively Regulates T-cell Activation**

- CTLA4 (CD152) expression is induced by T-cell activation
- CTLA4 is structurally similar to CD28
- CTLA4 binds CD80/86 with greater avidity than CD28
- CTLA4 negatively regulates T-cell activation

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**Early preclinical transplant studies utilized CTLA4Ig to block B7-CD28 costimulation**

- CTLA4 (CD152)
  - A human trans-membrane protein
- CTLA4Ig
  - Human fusion protein
- IgG1
  - A human antibody

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Belatacept potently and selectively blocks T-cell activation

- No cell division
- No cytokine production
- Anergy
- Apoptosis.

Belatacept: Phase 3 Studies in *de novo* Renal Transplantation

- **IM103-008 (BENEFIT; Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial)**
  - Living or deceased donor
  - First-time recipient: PRA < 50%
  - Retransplant: PRA < 30%

Belatacept: Phase 3 Studies in *de novo* Renal Transplantation

- **IM103-027 (BENEFIT-EXT; Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial)**
  - Deceased donor meeting extended criteria donor (ECD) criteria
  - First-time kidney transplants
  - PRA < 30%

Treatment Regimen

**BENEFIT -008 and BENEFIT-EXT -027**

<table>
<thead>
<tr>
<th>Transplantation</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine* (7±3 mg/kg daily)</td>
<td>150-300 100-250 ng/mL</td>
</tr>
<tr>
<td>Belatacept MI* (More Intensive)</td>
<td>10 mg/kg 5 mg/kg</td>
</tr>
<tr>
<td>Belatacept LI* (Less Intensive)</td>
<td>10 mg/kg 5 mg/kg</td>
</tr>
</tbody>
</table>

*All patients received basiliximab induction, mycophenolate mofetil, and corticosteroid-taper.
Phase 3 Studies

Co-primary Endpoints — 12 Months

- Composite patient and graft survival (non-inferiority; 10% margin)
- Composite renal impairment (superiority)
- Acute rejection (Study -008: non-inferiority, 20% margin)

Belatacept Phase 3 Clinical Trials Primary Endpoint:
Composite Renal Impairment

mGFR <60 mL/min/1.73m² OR Decreased mGFR ≥10 mL/min/1.73m² between months 3 and 12

Calculated GFR Over Time: BENEFIT

\[\text{Slope (95\%CI), mL/min/1.73 m²/\text{year}}\]

- Belatacept MI: +1.32 (0.07, 2.58)
- Belatacept LI: +1.22 (-0.01, 2.44)
- Cyclosporine: -1.96 (-3.22, -0.70)

Calculated GFR Over Time: BENEFIT-EXT

\[\text{Slope (95\%CI), mL/min/1.73 m²/\text{year}}\]

- Belatacept MI: -0.59 (-2.07, 0.90)
- Belatacept LI: -0.85 (-2.32, 0.62)
- Cyclosporine: -2.01 (-3.49, -0.53)
Belatacept Phase 3 Clinical Trial Results: Incidence of Acute Rejection

<table>
<thead>
<tr>
<th>Banff Grade</th>
<th>BENEFIT</th>
<th>BENEFIT-EXT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild acute (IA)</td>
<td>7(3)</td>
<td>20(9)</td>
</tr>
<tr>
<td>Mild acute (IB)</td>
<td>8(4)</td>
<td>4(2)</td>
</tr>
<tr>
<td>Moderate acute (IIA)</td>
<td>16(7)</td>
<td>17(10)</td>
</tr>
<tr>
<td>Moderate acute (IIIB)</td>
<td>11(2)</td>
<td>8(5)</td>
</tr>
<tr>
<td>Severe Acute (III)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Did not meet 20% NI margin
* Met 20% NI margin

Both belatacept groups met 20% NI margin vs. CsA

Worse Graft Outcomes
- High Banff grade
- Associated with anti-HLA antibodies
- Late
- Recurrent
- Poor renal function after rejection

Better Graft Outcomes
- Low Banff grade
- Not associated with anti-HLA antibodies
- Early
- Single
- Good renal function after rejection

Prognostic Features of Rejection Episodes

Phase 3 Studies; ITT Population; Year 1 DBL

Prevalence of CAN / IFTA at Month 12

Belatacept and CV Risk Factors
# Summary of the Phase III Belatacept Trials

- **LI has better overall safety profile than MI and is the recommended registered regimen.**

- The risk of PTLD is minimized by selecting patients who are known to be EBV + and reversing episodes of acute rejection with steroid rather than antilymphocyte agents.
Immunosuppression with Belatacept-Based, CNI-Avoiding and Steroid-Avoiding Regimens vs a Tacrolimus-Based, Steroid-Avoiding Regimen in Kidney Transplant Patients: Results of a 1-Year, Randomized Study

Ronald Ferguson, Flavio Vincenti, Dixon B Kaufman, E Steve Woodle, Brad A Marder, Franco Citterio, William Marks, Mamta Agarwal, Yuping Dong, Pushkal Garg, Josep Grinyó

Study Design (Exploratory, Phase II)
Randomized, open-label, multicenter study of belatacept-based steroid-avoiding regimens

Primary Clinical Endpoint
1 month 3 months 6 months 1 year LTE 3 years

Thymoglobulin + Belatacept + MMF
N = 33

De novo renal Tx

Thymoglobulin + Belatacept + Sirolimus
N = 26

Thymoglobulin + Tacrolimus + MMF
N = 30

Acute Rejection by Month 12

<table>
<thead>
<tr>
<th>Renf grade, n (%)</th>
<th>Belatacept + MMF</th>
<th>Belatacept + SRL</th>
<th>TAC + MMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild acute (IA)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mild acute (IB)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Moderate acute (IA)</td>
<td>2 (6)</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Moderate acute (II)</td>
<td>1 (3)</td>
<td>1 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Severe acute (III)</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Biopsies were read centrally

Mean MDRD GFR Over Time

Belatacept + MMF: 62 mL/min
Belatacept + SRL: 54 mL/min
Tacrolimus + MMF: 54 mL/min
Patients Steroid-free by Month 12

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belatacept+MMF (n = 33)</td>
<td>75</td>
</tr>
<tr>
<td>Belatacept+SRL (n = 26)</td>
<td>77</td>
</tr>
<tr>
<td>TAC+MMF (n = 30)</td>
<td>93</td>
</tr>
</tbody>
</table>

Belatacept Monotherapy (ITN Trial)

- **Daclizumab**
- **Steroids**
- **Sirolimus (8-12 μg/mL)**

Belatacept - 10 mg/kg at day 0, 4, weeks 2, 4, 8 and 12. Then, 5 mg/kg monthly.

Day 0 Transplant

S.Creat. mg/dL

- 5.7
- 1.2
- 1.2
- 1.2
- 1.0

59-year old with Type II diabetes. Kidney biopsy at one year was normal. No presence of DSA.

TASOCITINIB (CP690,550)
A JANUS Kinase 3 Inhibitor

CP690,550

The JANUS KINASES

JAK1  JAK2  JAK3  Tyk2

Roman God of Gates
Cytokine receptors that share γc subunit and their functions

- IL-2R
- IL-4R
- IL-7R
- IL-9R
- IL-15R
- IL-21R

- Control of peripheral self-tolerance
- Development of T regulatory cells
- Differentiation of helper and cytotoxic T cells
- In-vitro expansion and differentiation of antigen-activated T and NK cells
- Regulation of B cell function in concert with IL-2
- Immunoglobulin class switching
- T-lymphocyte development and survival of T cells
- Growth and survival of B-cell progenitors (mice)
- Expansion of NK cells
- Homestasis of peripheral T cells
- Homestasis of peripheral B cells
- Expansion of CD8 memory cells
- Inhibition of γc
- Regulation of immunoglobulin production

- JAK inhibition suppresses signaling of multiple cytokines including IL-2, IL-4, IL-7, IL-9, IL-15, IL-21

Mutations of the γc Chain or JAK3 Result in Severe Combined Immunodeficiency

- IL-2, IL-4, IL-7
- IL-9, IL-15, IL-21

Inhibition of the γc/JAK3 pathway is likely to induce patient immunosuppression

Calcineurin-Inhibitor-Free Immunosuppression Based on the JAK Inhibitor CP-690,550: A Pilot Study in De Novo Kidney Allograft Recipients

- CP 30 mg bid
- BK & CMV
- CP 15 mg bid
- more favorable dose
**Study Design**

- **Screening Day -30 to 0**
- **Day 1 to Month 12**
  - **Transplant**
  - **CsA-ME**
  - **Tasocitinib**
    - 15 mg BID
    - 10 mg BID
  - **Extension**

**Primary efficacy endpoint** (non-inferiority vs. CsA, NI margin 12%)
- Biopsy-proven acute rejection (BPAR) rate at Month 6, or
- BPAR meeting Scr criteria at Month 6

**Primary safety endpoint** (superiority vs CsA)
- Measured GFR (iohexol serum clearance) at Month 6

**Patient Baseline Characteristics - As Treated**

<table>
<thead>
<tr>
<th>Sex, n (%)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tasocitinib 15 mg BID 1-6 months (n=105)</td>
<td>62 (79.1)</td>
<td>40 (74.6)</td>
</tr>
<tr>
<td>Tasocitinib 15 mg BID 1-3 months (n=107)</td>
<td>70 (64.2)</td>
<td>46 (85.5)</td>
</tr>
<tr>
<td>CsA (n=109)</td>
<td>60 (54.7)</td>
<td>48 (89.8)</td>
</tr>
</tbody>
</table>

**Mean age, years (SD)**
- Tasocitinib 15 mg BID 1-6 months: 48.1 (11.8)
- Tasocitinib 15 mg BID 1-3 months: 46.8 (12.6)
- CsA: 47.1 (12.9)

**Race, n (%)**
- White: 72 (86.8) vs 71 (85.4) vs 78 (71.6)
- Black: 13 (15.7) vs 21 (33.8) vs 12 (11.3)
- Asian: 3 (3.7) vs 1 (1.5) vs 10 (9.2)
- Other: 0 (0.0) vs 0 (0.0) vs 14 (12.9)

**Concurrent immunosuppressive agents across all arms**
- Basiliximab induction (days 0 and 4), MPA products (Cellcept or Myfortic), corticosteroid taper

**International study including 15 countries and 57 centers**

**Patient Disposition /Patient and Graft Survival**

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Tasocitinib 15 mg BID 1-6 months</th>
<th>Tasocitinib 15 mg BID 1-3 months</th>
<th>CsA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized and treated</td>
<td>105</td>
<td>107</td>
<td>109</td>
</tr>
<tr>
<td>Discontinued (all reasons)</td>
<td>44 (40.0)</td>
<td>45 (40.5)</td>
<td>28 (25.5)</td>
</tr>
<tr>
<td>Discontinued due to insufficient clinical response or acute rejection from study phase</td>
<td>13 (12.4)</td>
<td>11 (10.3)</td>
<td>12 (11.0)</td>
</tr>
<tr>
<td>6-month patient survival (%)</td>
<td>98.1</td>
<td>99.1</td>
<td>97.2</td>
</tr>
<tr>
<td>6-month graft survival (%)</td>
<td>96.2</td>
<td>96.3</td>
<td>96.3</td>
</tr>
</tbody>
</table>

**Primary Efficacy Endpoints:**

- **BPAR and BPAR meeting Scr criteria at Month 6**
  - Non-inferiority was demonstrated between each of the tasocitinib groups and CsA in BPAR and BPAR meeting Scr criteria.
Infections and Post-Transplant Lymphoproliferative Disorder

<table>
<thead>
<tr>
<th></th>
<th>Tasocitinib 15 mg BID 1-6 months</th>
<th>Tasocitinib 15 mg BID 1-3 months</th>
<th>CsA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically significant infection at Month 6, %</td>
<td>41.7</td>
<td>42.5</td>
<td>38.4</td>
</tr>
<tr>
<td>Serious infection at Month 6, %</td>
<td>35.2</td>
<td>29.9</td>
<td>22.0</td>
</tr>
<tr>
<td>6-month incidence of CMV disease including CMV syndrome, %</td>
<td>14.8</td>
<td>12.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Polymavus-associated nephropathy, %</td>
<td>2.45</td>
<td>2.39</td>
<td>0.95</td>
</tr>
<tr>
<td>Post-transplant lymphoproliferative disorder (PTLD), n</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

All three PTLD cases occurred approximately 10 months post-transplant; 2/3 cases occurred after data cut-off date for the 6-month interim analysis.

Serious infection defined as an infection reported as a serious adverse event.

Hemoglobin and Absolute Neutrophil Counts

<table>
<thead>
<tr>
<th></th>
<th>Hemoglobin</th>
<th>Absolute Neutrophil Counts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Day 14</td>
</tr>
<tr>
<td>Tasocitinib 15 mg BID 1-6 months</td>
<td>15.1 ± 0.6</td>
<td>14.9 ± 0.5</td>
</tr>
<tr>
<td>Tasocitinib 15 mg BID 1-3 months</td>
<td>15.0 ± 0.5</td>
<td>14.8 ± 0.5</td>
</tr>
<tr>
<td>CsA</td>
<td>14.5 ± 0.5</td>
<td>14.3 ± 0.5</td>
</tr>
</tbody>
</table>

Serum Lipid Concentrations at Month 6

<table>
<thead>
<tr>
<th></th>
<th>Total cholesterol</th>
<th>LDL cholesterol</th>
<th>HDL cholesterol</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tasocitinib 15 mg BID 1-6 months</td>
<td>194.4</td>
<td>108.2</td>
<td>49.8</td>
<td>113.5</td>
</tr>
<tr>
<td>Tasocitinib 15 mg BID 1-3 months</td>
<td>192.5</td>
<td>106.9</td>
<td>50.1</td>
<td>113.3</td>
</tr>
<tr>
<td>CsA</td>
<td>190.6</td>
<td>106.3</td>
<td>50.2</td>
<td>112.8</td>
</tr>
</tbody>
</table>

New-onset Diabetes and Serum Lipids

K-M Rates of Patients with NODAT2 and NODAT2/IFG at Month 6

<table>
<thead>
<tr>
<th></th>
<th>K-M rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tasocitinib 11 mg BID 1-6 months</td>
<td>10.0 ± 1.2</td>
</tr>
<tr>
<td>Tasocitinib 15 mg BID 1-6 months</td>
<td>10.1 ± 1.2</td>
</tr>
<tr>
<td>Tasocitinib 15 mg BID 1-3 months</td>
<td>10.3 ± 1.2</td>
</tr>
<tr>
<td>CsA</td>
<td>11.0 ± 1.2</td>
</tr>
</tbody>
</table>

Blood Pressure and Use of Antihypertensive Medications at Month 6

<table>
<thead>
<tr>
<th></th>
<th>Systolic Blood Pressure</th>
<th>Diastolic Blood Pressure</th>
<th>Use of Antihypertensive Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tasocitinib 15 mg BID 1-6 months</td>
<td>128.4 ± 12.6</td>
<td>76.3 ± 7.4</td>
<td>74.3 ± 7.4</td>
</tr>
<tr>
<td>Tasocitinib 15 mg BID 1-3 months</td>
<td>126.4 ± 11.6</td>
<td>75.2 ± 7.3</td>
<td>76.2 ± 7.5</td>
</tr>
<tr>
<td>CsA</td>
<td>126.0 ± 11.0</td>
<td>75.0 ± 7.0</td>
<td>76.0 ± 7.0</td>
</tr>
</tbody>
</table>

Use of Antihypertensive Medications

<table>
<thead>
<tr>
<th></th>
<th>% Subjects Using Any Antihypertensive Meds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tasocitinib 15 mg BID 1-6 months</td>
<td>74.3 ± 7.4</td>
</tr>
<tr>
<td>Tasocitinib 15 mg BID 1-3 months</td>
<td>76.2 ± 7.5</td>
</tr>
<tr>
<td>CsA</td>
<td>76.0 ± 7.0</td>
</tr>
</tbody>
</table>

NODAT2: patients who required treatment for diabetes for ≥30 consecutive days or with fasting serum glucose ≥126 mg/dL.
IFG: defined as fasting serum glucose 110-125 mg/dL.
HDL, high-density lipoprotein; IFG, impaired fasting glucose.
LDL, low-density lipoprotein; NODAT, new-onset diabetes after transplantation.
Exposure-response analysis results: 6-month Kaplan-Meier rates by tacrolimus exposure

<table>
<thead>
<tr>
<th>Exposure</th>
<th>BCAR %</th>
<th>CMV disease, %</th>
<th>Serious infections, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tasocitinib group (divided into 2 groups of TWC2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (n=88)</td>
<td>10.5</td>
<td>3.5</td>
<td>18</td>
</tr>
<tr>
<td>High (n=88)</td>
<td>14</td>
<td>25.5</td>
<td>46</td>
</tr>
<tr>
<td>Tasocitinib group (divided into quartiles of TWC2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st quartile (n=44)</td>
<td>14</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>2nd quartile (n=44)</td>
<td>7</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>3rd quartile (n=44)</td>
<td>23</td>
<td>29</td>
<td>43</td>
</tr>
<tr>
<td>4th quartile (n=44)</td>
<td>5</td>
<td>22</td>
<td>49</td>
</tr>
<tr>
<td>CsA Group</td>
<td>19</td>
<td>3</td>
<td>20</td>
</tr>
</tbody>
</table>

Q1: 43-96; Q2: 96-122; Q3: 122-158; Q4: 158-397 ng/mL
CMV disease, CMV-related event or isolated CMV viremia reported as an adverse event
BCAR biopsy-confirmed acute rejection; CMV, cytomegalovirus; CsA, cyclosporine A; LDAR, locally diagnosed acute rejection; TWC2, time-weighted average tacrolimus concentration at 2 hours post-dose

Summary (6-month Interim Analysis)

- The primary objectives of the interim analysis were met as demonstrated by non-inferiority in the incidence of BPAR rates and statistically significantly higher measured GFR at Month 6 in each of the tacrolimus groups compared with the CsA control group.
- There was also evidence of over-immunosuppression (higher incidence of serious infections and opportunistic viral infections) and excessive myelosuppression (higher incidence of anemia, neutropenia, and leukopenia) in the tacrolimus groups compared with the CsA group. Lower dosage based on TDM may improve the safety without jeopardizing efficacy.
- There were trends for improved glycemic control and lower systolic and diastolic blood pressures in the tacrolimus groups, compared with the CsA group.

CONCLUSION

- The past decade has not witnessed the approval of a new drug in transplantation.
- The drugs in the new pipeline provide efficacy while preserving renal function, decreasing CV risk factors and the promise of improving long term outcome.