Rapid and Robust B Cell Depletion in Preliminary Results of a Phase 2 Study of Ublituximab, Novel Glycoengineered Anti-CD20 Mab, RMS Patients

Amy Lovett-Racke, PhD
May 26, 2017
Go to slide master view and add unique titles to all slides. They will not be visible, but will be used by screen reader.
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- National Institutes of Health
- National Multiple Sclerosis Society
- Strategic Pharmaceutical Academic Research Consortium
Ublituximab (TG-1101) is a novel, chimeric monoclonal antibody (mAb) targeting a unique epitope on the CD20 antigen, and glycoengineered to enhance affinity for all variants of FcγRIIIa receptors, thereby demonstrating greater antibody-dependent cellular cytotoxicity (ADCC) activity than rituximab and ofatumumab.
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Background

- Ublituximab (TG-1101) is a novel, chimeric monoclonal antibody (mAb) targeting a unique epitope on the CD20 antigen, and glycoengineered to enhance affinity for all variants of FcγRIIIa receptors, thereby demonstrating greater antibody-dependent cellular cytotoxicity (ADCC) activity than rituximab and ofatumumab.

- Ublituximab was originally developed for B cell lymphomas, in response to the need for enhanced potency to deplete malignant B-cells with reduced expression of CD20, that are able to evade depletion via standard anti-CD20 therapies.

- To date, over 500 oncology patients have been treated with ublituximab, alone and in combination with other agents, and two large Phase III trials (UNITY and GENUINE) for B cell lymphomas are currently underway. Completed studies have demonstrated robust effects on all endpoints and excellent safety and tolerability.

- Evidence for the role of B cells in the pathogenesis of Multiple Sclerosis and the marked efficacy of anti-CD20s tested thus far prompted us to conduct TG1101 RMS201, a Phase IIa proof of concept study in relapsing MS.
Objective

- TG1101 RMS201 (clinicaltrials.gov NCT02738775) is a randomized, placebo controlled, multi-center study to test the safety and efficacy of ublituximab, at doses markedly less than used in ongoing Phase 3 oncology studies, and at a range of infusion times, with a goal of rapid infusions.

- Primary endpoint is the Responders Rate, defined as percent of subjects with ≥95% reduction in peripheral CD19+ B-cells within 2 weeks after the second infusion (day 15).

- The TG1101 RMS201 study is ongoing and will incorporate additional clinical and MRI measures (see Study Design). We report preliminary results of B cell depletion after the second infusion.
Study Design
### Study Design

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Subjects and treatment</th>
<th>Day 1/ infusion time</th>
<th>Day 15/ infusion time</th>
<th>Week 24/ infusion time</th>
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<tbody>
<tr>
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<td>Placebo / 4h</td>
<td>Placebo / 3h</td>
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<tr>
<td></td>
<td>UTX (n=6)</td>
<td>150 mg / 4h</td>
<td>450 mg / 3h</td>
<td>450 mg / 1.5h</td>
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<td>Placebo / 4h</td>
<td>Placebo / 1.5h</td>
<td>-</td>
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<tr>
<td></td>
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<td>150 mg / 4h</td>
<td>450 mg / 1.5h</td>
<td>450 mg / 1h</td>
</tr>
<tr>
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<td>Placebo (n=2)</td>
<td>Placebo / 4h</td>
<td>Placebo / 1h</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>UTX (n=6)</td>
<td>150 mg / 4h</td>
<td>450 mg / 1h</td>
<td>600 mg / 1h</td>
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</tbody>
</table>
### Study Design

Three additional cohorts have been added to further reduce infusion times to 1 hr.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Subjects and treatment</th>
<th>Day 1/ infusion time</th>
<th>Day 15/ infusion time</th>
<th>Week 24/ infusion time</th>
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<tr>
<td></td>
<td>UTX (n=6)</td>
<td>150 mg / 4h</td>
<td>450 mg / 1h</td>
<td>600 mg / 1h</td>
</tr>
<tr>
<td>Cohort</td>
<td>Subjects and Treatment</td>
<td>Age (Years)(^1)</td>
<td>Gender (% Female)</td>
<td>Disease Duration (Years)(^{1,2})</td>
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<tr>
<td>--------</td>
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<td>---------------------------------</td>
</tr>
<tr>
<td>1</td>
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<td>39±14</td>
<td>50%</td>
<td>15.5±20.4</td>
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<tr>
<td></td>
<td>UTX (n=6)</td>
<td>43±12</td>
<td>67%</td>
<td>7.1±7.3</td>
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<tr>
<td>2</td>
<td>Placebo (n=2)</td>
<td>44±1</td>
<td>0%</td>
<td>0.9±1.2</td>
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<tr>
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<td>33±10</td>
<td>100%</td>
<td>5.3±6.4</td>
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<td>38±7</td>
<td>50%</td>
<td>11.5±7.5</td>
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<td>UTX (n=6)</td>
<td>40±11</td>
<td>67%</td>
<td>13.4±10.0</td>
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<tr>
<td>Total</td>
<td>n=24</td>
<td>40±11</td>
<td>67%</td>
<td>8.8±9.0</td>
</tr>
</tbody>
</table>

\(^1\) Mean ± Standard Deviation

\(^{2}\) Distribution of times from diagnosis: 11 subjects (45.8%) were less than 5 years, 7 (29.2%) were 5-10 years, and 6 (25%) were greater than 10 years.
Blood is collected in heparinized tubes and shipped to OSU.

Blood

Centrifuge 400 x g 50 Minutes

Plasma
Lymphocytes
Monocytes
Erythrocytes

Ficoll

B Cell
CD19 CD27 CD5

T Cell

Monocyte
NK Cell
B Cell
T Cell
B Cell

Flow Cytometry

Sample (stained cells in suspension)
Hydrodynamic Focussing
Cells pass through in single file
Sheath fluid
Laser light source

Forward and side scattered light from all cells detected

Primary antibodies from the same species
Proteins

B Cell
Blood is collected in heparinized tubes and shipped to OSU.

Blood

<table>
<thead>
<tr>
<th>Ficoll</th>
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</thead>
<tbody>
<tr>
<td>Plasma</td>
</tr>
<tr>
<td>Lymphocytes</td>
</tr>
<tr>
<td>Monocytes</td>
</tr>
<tr>
<td>Erythrocytes</td>
</tr>
</tbody>
</table>

B Cell

CD19
CD27
CD5

B Cell

T Cell

B Cell

T Cell

Monocyte

NK Cell

T Cell

B Cell

Dendritic Cell

Flow Cytometry

Sheath fluid

Sample (stained cells in suspension)

Hydrodynamic focusing

Cells pass through 'single file'

Fluorescence emitted from stained cells detected

Forward and side scattered light from all cells detected

Laser light source
<table>
<thead>
<tr>
<th>B/NK Cell Panel</th>
<th>Activated/Reg B Cell Panel (PMA/Ion/CpG)</th>
</tr>
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<tbody>
<tr>
<td>CD3</td>
<td>CD3</td>
</tr>
<tr>
<td>CD19</td>
<td>CD19</td>
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<td>CD5</td>
<td>CD5</td>
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<tr>
<td>CD1d</td>
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<td>CD27</td>
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<tr>
<td>CD56</td>
<td>IL-10</td>
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<tr>
<td>CD16</td>
<td>IL-27/35</td>
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</table>

<table>
<thead>
<tr>
<th>T Cell Panel</th>
<th>Treg Cell Panel</th>
<th>Helper T Cell Panel (PMA/Ion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3</td>
<td>CD3</td>
<td>CD3</td>
</tr>
<tr>
<td>CD4</td>
<td>CD4</td>
<td>CD4</td>
</tr>
<tr>
<td>CD8</td>
<td>CD25</td>
<td>CD45RA</td>
</tr>
<tr>
<td>CD45RA</td>
<td>FoxP3</td>
<td>IL-10</td>
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<tr>
<td>CD27</td>
<td></td>
<td>IFNγ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GM-CSF</td>
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<tr>
<td></td>
<td></td>
<td>IL-17</td>
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</table>
B Cell Analysis

B Cells

T Cells
B Cell Analysis

Placebo Phase

*Screen*
- **SSC**
- **FSC**
- **CD19** 7.0%
- **CD3**

*Day 0*
- **SSC**
- **FSC**
- **CD19**
- **CD3** 6.5%

*Day 1*
- **SSC**
- **FSC**
- **CD19**
- **CD3** 10.3%

*Week 2*
- **SSC**
- **FSC**
- **CD19**
- **CD3** 10.2%

*Week 3*
- **SSC**
- **FSC**
- **CD19**
- **CD3** 5.3%

*Week 4*
- **SSC**
- **FSC**
- **CD19**
- **CD3** 9.4%
B Cell Analysis

Placebo Phase

- Screen: 7.0%
- Day 0: 6.5%
- Day 1: 10.3%
- Week 2: 10.2%
- Week 3: 5.3%
- Week 4: 9.4%

Treatment Phase

- Screen: 8.9%
- Day 0: 9.9%
- Day 1: 0%
- Week 2: 0%
- Week 3: 0%
- Week 4: 9.4%
# B Cell Analysis

<table>
<thead>
<tr>
<th></th>
<th>Placebo Phase</th>
<th>Treatment Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screen</strong></td>
<td>FSC</td>
<td>FSC</td>
</tr>
<tr>
<td><strong>Day 0</strong></td>
<td>CD19</td>
<td>CD19</td>
</tr>
<tr>
<td><strong>Day 1</strong></td>
<td>CD19</td>
<td>CD19</td>
</tr>
<tr>
<td><strong>Week 2</strong></td>
<td>CD19</td>
<td>CD19</td>
</tr>
<tr>
<td><strong>Week 3</strong></td>
<td>CD19</td>
<td>CD19</td>
</tr>
<tr>
<td><strong>Week 4</strong></td>
<td>CD19</td>
<td>CD19</td>
</tr>
</tbody>
</table>

**Placebo Phase**
- Day 0: 6.5% CD19
- Day 1: 10.3% CD19
- Week 2: 10.2% CD19
- Week 3: 5.3% CD19
- Week 4: 9.4% CD19

**Treatment Phase**
- Day 0: 8.9% CD19
- Day 1: 9.9% CD19
- Week 2: 0% CD19
- Week 3: 0% CD19
- Week 4: 0% CD19
B Cell Analysis

B Cell Analysis in Placebo and Treatment Phase

% B Cells

Cohort 1 - F
Cohort 2 - C
Cohort 2 - G
Cohort 3 - C
Cohort 3 - D
B Cell Analysis

Change in % B Cells with Ublituximab

*** p<0.001 Bonferroni’s Multiple Comparison Test compared to Screening and Day 0
*No statistical difference (ANOVA) between cohorts at each time point. Error bars are mean±SEM.

All patients received the same total dose of 600 mg, only infusion times differed.
B Cell Analysis

Six Month Analysis of B Cells

Arrows represent treatment timepoints. Blood analysis was done pre-treatment.
Arrows represent treatment timepoints. Blood analysis was done pre-treatment.
T Cell Analysis

Placebo Phase

Day 0
- Screen
  - CD19
  - FSC
  - 60%
  - CD3
  - 7.0%

Day 1
- CD19
- FSC
- 10.3%
- CD3
- 44%

Week 2
- CD19
- FSC
- 10.2%
- CD3
- 60%

Week 3
- CD19
- FSC
- 5.3%
- CD3
- 32%

Week 4
- CD19
- FSC
- 9.4%
- CD3
- 58%
T Cell Analysis

Placebo Phase vs Treatment Phase

**Screen**
- SSC
- CD19
- FSC
- CD3

**Day 0**
- SSC
- CD19
- FSC
- CD3

**Day 1**
- SSC
- CD19
- FSC
- CD3

**Week 2**
- SSC
- CD19
- FSC
- CD3

**Week 3**
- SSC
- CD19
- FSC
- CD3

**Week 4**
- SSC
- CD19
- FSC
- CD3

**Day 0**
- 7.0%
- 57%
- 6.5%
- 44%

**Day 1**
- 10.3%
- 36%
- 10.2%
- 55%

**Week 2**
- 60%
- 32%
- 58%
- 9.4%

**Week 3**
- 9.4%
- 58%

**Week 4**
- 8.9%
- 52%
- 9.9%
T Cell Analysis

Placebo Phase

<table>
<thead>
<tr>
<th>Phase</th>
<th>CD3 57%</th>
<th>Day 0 36%</th>
<th>Day 1 44%</th>
<th>Week 2 60%</th>
<th>Week 3 58%</th>
<th>Week 4 59%</th>
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</thead>
<tbody>
<tr>
<td>Screen</td>
<td>7.0%</td>
<td>6.5%</td>
<td>10.3%</td>
<td>10.2%</td>
<td>5.3%</td>
<td>9.4%</td>
</tr>
<tr>
<td>Day 0</td>
<td>57%</td>
<td>36%</td>
<td>44%</td>
<td>60%</td>
<td>32%</td>
<td>60%</td>
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<tr>
<td>Day 1</td>
<td>6.5%</td>
<td>36%</td>
<td>44%</td>
<td>60%</td>
<td>32%</td>
<td>60%</td>
</tr>
<tr>
<td>Week 2</td>
<td>10.3%</td>
<td>44%</td>
<td>60%</td>
<td>60%</td>
<td>32%</td>
<td>60%</td>
</tr>
<tr>
<td>Week 3</td>
<td>10.2%</td>
<td>44%</td>
<td>60%</td>
<td>60%</td>
<td>32%</td>
<td>60%</td>
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<tr>
<td>Week 4</td>
<td>5.3%</td>
<td>32%</td>
<td>60%</td>
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<td>32%</td>
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Treatment Phase

<table>
<thead>
<tr>
<th>Phase</th>
<th>CD3 8.9%</th>
<th>Day 0 70%</th>
<th>Day 1 52%</th>
<th>Week 2 59%</th>
<th>Week 3 60%</th>
<th>Week 4 48%</th>
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<tbody>
<tr>
<td>Screen</td>
<td>8.9%</td>
<td>70%</td>
<td>52%</td>
<td>59%</td>
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<td>48%</td>
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<tr>
<td>Day 0</td>
<td>70%</td>
<td>52%</td>
<td>59%</td>
<td>60%</td>
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<td>48%</td>
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<tr>
<td>Day 1</td>
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<tr>
<td>Week 2</td>
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<td>60%</td>
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<td>48%</td>
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<tr>
<td>Week 3</td>
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<td>60%</td>
<td>48%</td>
</tr>
<tr>
<td>Week 4</td>
<td>48%</td>
<td>48%</td>
<td>48%</td>
<td>48%</td>
<td>48%</td>
<td>48%</td>
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</tbody>
</table>
T Cell Analysis

- Cohort 3 - C
- Cohort 3 - D
- Cohort 1 - F
- Cohort 2 - C
- Cohort 2 - G

% T Cells

Time of Analysis

Cohort 1 - F
Cohort 2 - C
Cohort 2 - G
Cohort 3 - C
Cohort 3 - D
Analysis of % T Cells with Ublituximab Therapy

Statistical analysis with Bonferroni's Multiple Comparison Test
B Cell Subset Analysis

Screen

Day 0

Day 1

Week 2

Week 3

Week 4
B Cell Subset Analysis

Screen

Day 0

Day 1

Week 2

Week 3

Week 4

SSC  FSC  CD3  CD19  B Cells
B Cell Subset Analysis

Day 0

Day 1

Week 2

Week 3

Week 4

Screen
B Cell Subset Analysis

Screen

Day 0

Day 1

Week 2

Week 3

Week 4

SSC

FSC

CD3

CD19

CD27

FSC

Naive

Memory

B Cells

Naive

Memory

Naive

Memory

Naive

Memory

Memory

Naive

Memory

Memory

Naive

Memory

Memory

Naive

Memory

Memory

Naive

Memory
B Cell Subset Analysis

Day 0

Day 1

FSC

SSC

CD19

CD3

CD27

CD19

Naive

Memory

Naive

Memory
B Cell Subset Analysis

Naive versus Memory % B Cells

% B Cells

Naive Memory Naive Memory Naive Memory Naive Memory
--Screen/Day0-- -----Day 1----- -----Week 2----- -----Week 4-----
Ublituximab is well-tolerated, with only mild infusion reactions (Grade 1-2) being observed, even with infusion times reduced to 1 hour.

Ublituximab efficiently depletes B cells (98.9%), meeting the endpoint of >95% depletion within two weeks of second dose, comparable to ocrelizumab.

Although there is a transient decrease in T cells after the initial dose of ublituximab, T cell numbers are fairly stable over time.

Memory B cells seem slightly more resistant to depletion, but are efficiently depleted in all patients.

A comprehensive analysis of B and T cell profiles is being performed to understand how B cell depletion influences T cell profiles, and to characterize the B cell repletion.

This one year study of ublituximab in RMS patients is ongoing and clinical and MRI measures will be reported at future congresses.
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Wendy Su, PhD
James Eubanks, PhD