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

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  • National Institutes of Health
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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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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 in 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

Placebo Phase

Clinical Assessment
Lab
Radiological assessment
TG1101 Administration

Weeks
-4 0 4 8 12 16 20 24 28 32 36 40 44 48
### 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>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Placebo (n=2)</td>
<td>Placebo / 4h</td>
<td>Placebo / 3h</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>UTX (n=6)</td>
<td>150 mg / 4h</td>
<td>450 mg / 3h</td>
<td>450 mg / 1.5h</td>
</tr>
<tr>
<td>2</td>
<td>Placebo (n=2)</td>
<td>Placebo / 4h</td>
<td>Placebo / 1.5h</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>UTX (n=6)</td>
<td>150 mg / 4h</td>
<td>450 mg / 1.5h</td>
<td>450 mg / 1h</td>
</tr>
<tr>
<td>3</td>
<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>
</tr>
</tbody>
</table>
### Baseline Demographics

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Subjects and Treatment</th>
<th>Age (Years)&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Gender (% Female)</th>
<th>Disease Duration (Years)&lt;sup&gt;1,2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Placebo (n=2)</td>
<td>39±14</td>
<td>50%</td>
<td>15.5±20.4</td>
</tr>
<tr>
<td></td>
<td>UTX (n=6)</td>
<td>43±12</td>
<td>67%</td>
<td>7.1±7.3</td>
</tr>
<tr>
<td>2</td>
<td>Placebo (n=2)</td>
<td>44±1</td>
<td>0%</td>
<td>0.9±1.2</td>
</tr>
<tr>
<td></td>
<td>UTX (n=6)</td>
<td>33±10</td>
<td>100%</td>
<td>5.3±6.4</td>
</tr>
<tr>
<td>3</td>
<td>Placebo (n=2)</td>
<td>38±7</td>
<td>50%</td>
<td>11.5±7.5</td>
</tr>
<tr>
<td></td>
<td>UTX (n=6)</td>
<td>40±11</td>
<td>67%</td>
<td>13.4±10.0</td>
</tr>
<tr>
<td>Total</td>
<td>n=24</td>
<td>40±11</td>
<td>67%</td>
<td>8.8±9.0</td>
</tr>
</tbody>
</table>

<sup>1</sup> Mean ± Standard Deviation  
<sup>2</sup> 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
30 Minutes

Ficoll

Plasma
Lymphocytes
Monocytes
Erythrocytes

B Cell
CD19
CD27
CD5

T Cell
Monocyte
NK Cell
B Cell
T Cell

Flow Cytometry

Sample (stained cells in suspending)

Hydrodynamic Focusing
Cells pass through in ‘single file’

Fluorescence emitted from stained cells detected

Forward and side scattered light from all cells detected

B Cell

Primary antibodies from the same species

CD19
CD27
CD5

Proteins
Blood is collected in heparinized tubes and shipped to OSU.
### Immune Profiling

#### B/NK Cell Panel
- CD3
- CD19
- CD5
- CD1d
- CD27
- CD56
- CD16

#### CD3
- CD3
- CD19
- CD5
- CD1d
- CD27
- IL-10
- IL-27/35

#### CD4
- CD4
- CD25
- FoxP3

#### CD8
- CD27

#### CD45RA

#### CD27

#### Activated/Reg B Cell Panel (PMA/Ion/CpG)
- CD3
- CD19
- CD5
- CD1d
- CD27
- IL-10
- IL-27/35

#### T Cell Panel
- CD3
- CD4
- CD8
- CD45RA
- CD27

#### Helper T Cell Panel (PMA/Ion)
- CD3
- CD4
- CD45RA
- IL-10
- IFNγ
- GM-CSF
- IL-17
B Cell Analysis

SSC-A vs. FSC-A

CD19 vs. CD3

B Cells

T Cells
B Cell Analysis

Placebo Phase

<table>
<thead>
<tr>
<th>Day 0</th>
<th>Day 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen</td>
<td>7.0%</td>
<td>6.5%</td>
<td>10.3%</td>
<td>10.2%</td>
</tr>
<tr>
<td>6.5%</td>
<td></td>
<td>10.3%</td>
<td>5.3%</td>
<td>9.4%</td>
</tr>
</tbody>
</table>
B Cell Analysis

Placebo Phase

Day 0

Day 1

Week 2

Week 3

Week 4

Treatment Phase

Screen

Day 0

Day 1

Week 2

Week 3

Week 4

7.0%

6.5%

10.3%

10.2%

5.3%

9.4%

8.9%

9.9%

0%

0%

0%

0%
**B Cell Analysis**

### Placebo Phase

- **Day 0**: 7.0% Screen, 6.5% CD3
- **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

**FSC**

**CD3**
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.
T Cell Analysis

**Placebo Phase**

*Day 0*
- Screen: SSC 7.0%, CD19 57%, CD3 36%

*Day 1*
- Day 0: SSC 6.5%, CD19 44%

*Week 2*
- Week 1: SSC 10.3%, CD19 44%, CD3 60%

*Week 3*
- Week 2: SSC 10.2%, CD19 53%, CD3 32%

*Week 4*
- Week 3: SSC 5.3%, CD19 9.4%, CD3 58%

**Treatment Phase**

*Day 0*
- Screen: SSC 8.9%, CD19 70%

*Day 1*
- Day 0: SSC 9.9%, CD19 52%

*Week 2*
- Week 1: SSC 10.2%, CD19 70%

*Week 3*
- Week 2: SSC 5.3%, CD19 9.9%, CD3 0%

*Week 4*
- Week 3: SSC 9.4%, CD19 9.9%, CD3 0%
T Cell Analysis

**Placebo Phase**

- **Screen**
  - 7.0% Screen
  - 6.5% Screen

- **Day 0**
  - 70%
  - 57%
  - 36%

- **Day 1**
  - 8.9%
  - 10.3%
  - 44%

- **Week 2**
  - 10.2%
  - 5.3%
  - 60%

- **Week 3**
  - 9.4%
  - 58%
  - 32%

- **Week 4**
  - 9.9%

**Treatment Phase**

- **Day 0**
  - 70%
  - 52%
  - 27%

- **Week 2**
  - 59%
  - 0%

- **Week 3**
  - 59%
  - 0%

- **Week 4**
  - 48%
T Cell Analysis

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

**Time of Analysis**

- Screen
- Day 0
- P - Day 1
- P - Week 2
- P - Week 3
- P - Week 4
- Screen
- Day 0
- T - Day 1
- T - Week 2
- T - Week 3
- T - Week 4

**% T Cells**

- 0
- 25
- 50
- 75

**Days and Weeks**

- Day 0
- P - Day 1
- P - Week 2
- P - Week 3
- P - Week 4
- Screen
- Day 0
- T - Day 1
- T - Week 2
- T - Week 3
- T - Week 4

**Graph**

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

Analysis of % T Cells with Ublituximab Therapy

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

Day 0

Day 1
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 (99%), 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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