P6.348 Preliminary Results of Phase 2a Multicenter Study of Ublituximab (UTX), a Novel Glycoengineered Anti-CD20 Monoclonal Antibody (mAb), in Patients with Relapsing Forms of Multiple Sclerosis (RMS) Demonstrates Rapid and Robust B Cell Depletion

Amy Lovett-Racke[1] , Yue Liu[1], Matthew Gormley[1], Michael Racke[2], Richard Shubin[3], Sibyl Wray[4], Wendy Su[5], James L. Eubanks[5], Edward Fox[6]

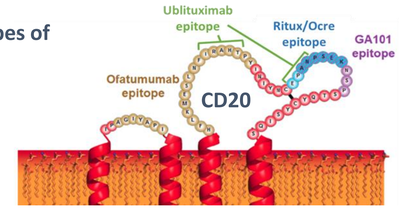
[1]Microbial Infection and Immunity, The Ohio State University, [2]The Ohio State University Medical Center, Wexner Medical Center, [3]Arcadia Neurology Center, [4]Hope Neurology, [5]TG Therapeutics, Inc., [6]Central Texas Neurology Consultants

Background

Ublituximab

- Ublituximab (TG-1101) is a novel chimeric monoclonal antibody (mAb) targeting a unique epitope on the CD20 antigen, 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 either alone or in combination with other agents, and two large international Phase III trials (UNITY and GENUINE) for B-cell lymphomas are currently underway. Studies in oncology to date have demonstrated robust B-cell depletion and a well tolerated safety profile, including in long-term follow-up, and dosing for 2+ years
- Evidence for the role of B-cells in the pathogenesis of Multiple Sclerosis and the success of anti-CD20s tested thus far, prompted the exploration of ublituximab in a Phase IIa proof-of-concept study in relapsing MS

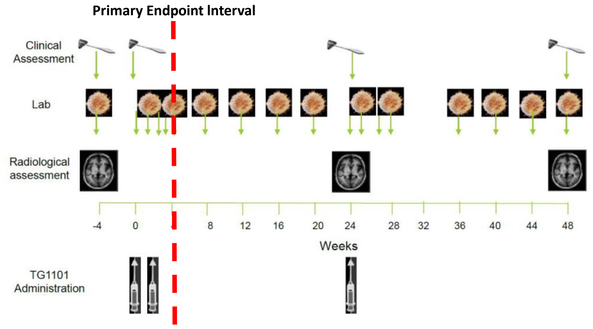
Binding Epitopes of Anti-CD20 Antibodies



Objectives

- TG1101-RMS201 (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)
- Additional clinical and radiological measures of efficacy are being evaluated. Herein we report preliminary results of B-cell depletion after the second infusion

Study Design



Cohort	Randomization: Subjects and treatment	Treatment Period: Day 1/ infusion time	Treatment Period: Day 15/ infusion time	Treatment Period: Week 24/ infusion time
1	Placebo (n=2)	Placebo / 4h	Placebo / 3h	-
	UTX (n=6)	150 mg / 4h	450 mg / 3h	450 mg / 1.5h
2	Placebo (n=2)	Placebo / 4h	Placebo / 1.5h	-
	UTX (n=6)	150 mg / 4h	450 mg / 1.5h	450 mg / 1h
3	Placebo (n=2)	Placebo / 4h	Placebo / 1h	-
	UTX (n=6)	150 mg / 4h	450 mg / 1h	600 mg / 1h

- Patients were enrolled sequentially in treatment cohorts 1, 2 and 3 and randomized 3:1 to ublituximab or placebo
- Ublituximab or placebo was administered via intravenous infusion at the doses and rates shown
- Patients randomized to placebo received a corresponding volume of normal saline (250 ml) for the first two infusions (at study days 1 and 15) and were observed for two additional weeks
- At study day 28, placebo patients were unblinded and, after re-screening, received the active drug and assessments as shown above
- Peripheral blood samples were collected at screening, first day of treatment (Day 1, Pre-dose), Day 2, Week 2, Week 3 (Day 15, Pre-dose), and Week 4
- Peripheral blood mononuclear cells were isolated via Ficoll. The cells were stained for CD19 (B-cell marker), CD3 (T-cell marker) and CD27 (memory B-cell marker), and analyzed on a BD FacsCanto II. The entire myeloid/lymphoid population was selected for analysis
- An Independent Data Safety Monitoring Board (DSMB) reviewed laboratory and clinical safety data from the first two subjects of each cohort (one ublituximab and one placebo) before allowing the study to continue

Results

Patient Population and Safety

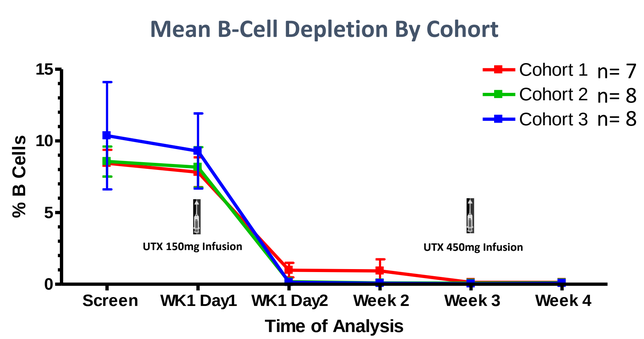
Baseline Demographics

Cohort	Subjects and Treatment	Age (Years)[1]	Gender (% Female)	Disease Duration (Years)[1,2]
1	Placebo (n=2)	39±14	50%	15.5±20.4
	UTX (n=6)	43±12	67%	7.1±7.3
2	Placebo (n=2)	44±1	0%	0.9±1.2
	UTX (n=6)	33±10	100%	5.3±6.4
3	Placebo (n=2)	38±7	50%	11.5±7.5
	UTX (n=6)	40±11	67%	13.4±10.0
Total	N=24	40±11	67%	8.8±9.0

[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.

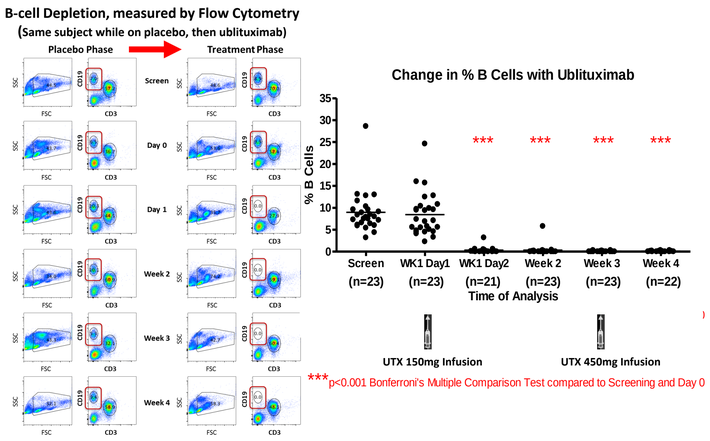
- The DSMB reviewed safety data for each cohort and approved continuation of the study at each safety review based on acceptable safety measures
- No Adverse Events (AEs) Grade >2 have been reported, with median time on the study of 5 months
- No infections have been reported to date
- Most frequent AEs were infusion related reactions; all were limited to Grade ≤ 2 on the Common Terminology of Adverse Events (CTCAE) scale, requiring minimal intervention or delay to date
- All scheduled doses were fully delivered to all subjects to date

Efficacy

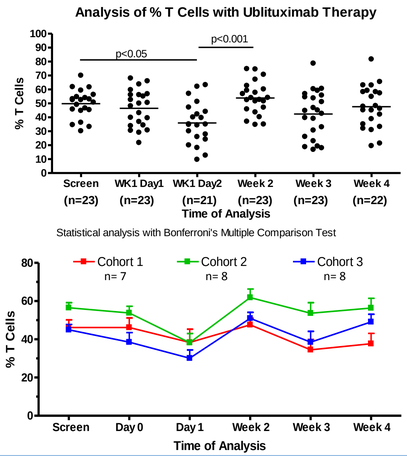


*No statistical difference (ANOVA) between cohorts at each time point. Error bars are mean±SEM.

All patients met primary end point of >95% B cell depletion by 4 weeks. The median B-cell depletion at Week 4 was 99%



***p<0.001 Bonferroni's Multiple Comparison Test compared to Screening and Day 0



The percentage of T cells in the myeloid/lymphoid population also declined transiently after Ublituximab treatment, but recovered by Week 2

Conclusions

- **In patients with relapsing MS, treatment with ublituximab resulted in a median 99% depletion of B-cells after two infusions with a cumulative dose of 600mg**
  - **This is comparable to previous reports for ocrelizumab and rituximab[3,4]**
- **Most commonly reported AEs were infusion related reactions (Grade ≤2) with a median time on study of 5 months**
- **Infusion times as low as one hour were well tolerated**
- **This one year study of ublituximab in RMS patients is ongoing, with clinical and MRI measures expected to be reported at future congresses**

[1] De Romeuf, C, et al British Journal of Haematology, 140, 635–643 (2008); [2] Leandro, MJ, Arthritis Res Ther 15, S3 (2013); [3] Kappos, L et al., Lancet Vol. 378, 1779-1787 (2011); [4] Hauser, SL et al., NEJM 358, 676-688 (2008)

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