MSDA Test Reveals Distinct Disease Activity Trajectories for Ublituximab and Teriflunomide in ULTIMATE I and II Trials

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Introduction

Ublituximab is a glycoengineered anti-CD20 monoclonal antibody approved for the treatment of relapsing forms of multiple sclerosis based on data from the ULTIMATE I & II phase 3 Trials for which the active comparator arm was Teriflunomide [1]. The Multiple Sclerosis Disease Activity Test (MSDA) is an analytically and clinically validated multi-protein assay that measures 18 protein biomarkers and utilizes an algorithm to determine an overall Disease Activity (DA) score and 4 Disease Pathway Scores [1, 2].

Objectives

To evaluate differences in the trajectories of the overall DA Score, 4 Pathway Scores (Immunomodulation, Neuroinflammation, Myelin Biology and Neuroaxonal Integrity) and 18 individual proteins in 81 patients treated with either ublituximab or teriflunomide over a 96-week period across up to 4 timepoints: Week 0, Week 24, Week 48 and Week 96. Additionally, performance of the MSDA algorithm was evaluated relative to radiographic and clinical disease activity endpoints that were utilized to clinically validate the MSDA test.

A) Ublituximab Treatment Arm

		0	24	48	96
n		61	61	61	59
Sex, n (%)	F	38 (62.3)	38 (62.3)	38 (62.3)	36 (61.0)
	M	23 (37.7)	23 (37.7)	23 (37.7)	23 (39.0)
GD+ >= 1, n (%)	0	28 (45.9)	60 (98.4)	60 (98.4)	59 (100.0)
	1+	33 (54.1)		1 (1.6)	
	Unknown		1 (1.6)		
NE_T2 >= 1, n (%)	Unknown	61 (100.0)	1 (1.6)		
	0		33 (54.1)	59 (96.7)	58 (98.3)
	1+		27 (44.3)	2 (3.3)	1 (1.7)
Active/Stable, n (%)	Active	33 (54.1)	27 (44.3)	2 (3.3)	1 (1.7)
	Stable	28 (45.9)	34 (55.7)	59 (96.7)	58 (98.3)
Relapse +/- 30 days, n (%)	No	58 (95.1)	61 (100.0)	61 (100.0)	59 (100.0)
	Yes	3 (4.9)			
Age, mean (SD)		38.6 (8.9)	39.1 (8.9)	39.5 (8.9)	40.1 (8.8)
DA Score, mean (SD)		6.5 (2.0)	2.7 (1.3)	2.2 (1.2)	1.9 (0.8)
Neuroinflammation, mean (SD)		7.3 (2.2)	2.3 (1.3)	1.9 (1.4)	1.5 (0.8)
Myelin Biology, mean (SD)		5.9 (1.8)	3.9 (1.7)	3.4 (1.3)	3.9 (1.2)
Immunomodulation, mean (SD)		6.9 (2.2)	2.1 (1.2)	1.8 (1.3)	1.3 (0.6)
Neuroaxonal Integrity, mean (SD)		5.5 (2.9)	3.0 (2.0)	2.5 (1.6)	2.3 (1.3)

B) Teriflunomide Treatment Arm

		0	24	48	96
n		20	20	20	20
Sex, n (%)	F	14 (70.0)	14 (70.0)	14 (70.0)	14 (70.0)
	M	6 (30.0)	6 (30.0)	6 (30.0)	6 (30.0)
GD+ >= 1, n (%)	0	9 (45.0)	9 (45.0)	13 (65.0)	12 (60.0)
	1+	11 (55.0)	11 (55.0)	7 (35.0)	8 (40.0)
	Unknown	20 (100.0)			
NE_T2 >= 1, n (%)	0		6 (30.0)	4 (20.0)	4 (20.0)
	1+		14 (70.0)	16 (80.0)	16 (80.0)
Active/Stable, n (%)	Active	11 (55.0)	14 (70.0)	16 (80.0)	16 (80.0)
	Stable	9 (45.0)	6 (30.0)	4 (20.0)	4 (20.0)
Relapse +/- 30 days, n (%)	No	20 (100.0)	18 (90.0)	20 (100.0)	19 (95.0)
	Yes		2 (10.0)		1 (5.0)
Age, mean (SD)		34.8 (11.4)	35.2 (11.4)	35.7 (11.4)	36.6 (11.4)
DA Score, mean (SD)		5.6 (1.9)	5.8 (1.8)	5.8 (1.5)	5.5 (2.0)
Neuroinflammation, mean (SD)		5.2 (2.2)	5.2 (1.9)	5.1 (1.4)	4.9 (2.0)
Myelin Biology, mean (SD)		6.2 (1.8)	6.5 (1.5)	6.5 (1.9)	6.5 (2.2)
Immunomodulation, mean (SD)		5.6 (2.2)	5.5 (2.1)	5.3 (1.7)	4.9 (2.2)
Neuroaxonal Integrity, mean (SD)		5.4 (2.4)	6.1 (2.3)	6.2 (2.4)	5.5 (2.7)

Table 1: Demographic Information, grouped by timepoint for A) Ublituximab and B) Teriflunomide

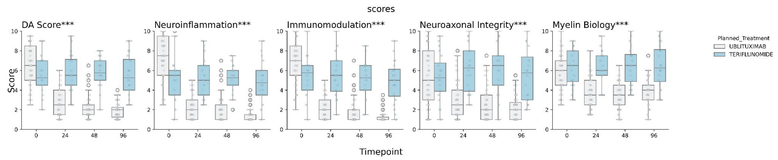

Figure 1: Boxplots of the Overall DA score and the 4 pathway scores over the 4 different timepoints (0, 24, 48, 96 months) by treatment arm. *** = significant after Bonferroni correction

Methods

322 serum samples from 81 ULTIMATE study participants representing up to 4 timepoints (Baseline, 24 weeks, 48 weeks, and 96 weeks) were assayed in the MSDA Test. 61 study participants were treated with ublituximab (intervention arm) and 20 participants were treated with teriflunomide (control arm). For two of the 61 patients in the ublituximab arm, the Week 96 sample was not available. All blood draws were performed prior to the ublituximab or corresponding IV placebo administration associated with each of the timepoints.

The MSDA test is reported on a scale of 1.0 -10.0 and has validated ranges established for Low (1.0 - 4.0), Moderate (4.5 -7.0) and High (7.5 -10.0) levels of disease activity. Samples from each treatment group and timepoint were categorized and compared according to their overall DA Score level.

The average treatment effect, holding baseline value, sex, and age constant, on the DA score, 4 Pathway Scores, and 18 individual log protein concentrations after demographic correction was estimated using linear mixed effects models. For each model, the biomarker endpoint was the dependent variable, and independent variables included treatment arm, biomarker endpoint baseline value, sex, and age. Random intercepts corresponding to the study participant were also included.

Area Under the receiver operating Curve (AUC) analysis was performed for the DA Score model to evaluate prediction performance in each treatment arm for: T1 gadolinium (Gd+) lesions, new or enlarging (N/E) T2 lesions, and active/stable status (composite variable combining clinical relapse, Gd+ and N/E T2 lesions).

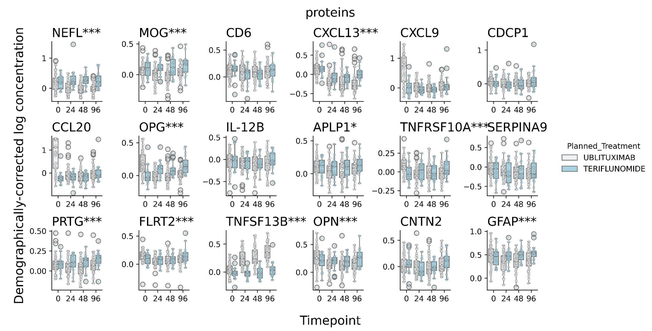

Figure 2: Boxplots of the 18 protein log concentrations (after demographic correction) over the 4 different timepoints (0, 24, 48, 96 months) by treatment arm. * = nominally significant, *** = significant after Bonferroni correction

Ublituximab Treatment Arm

DA Score Category	Baseline (n=61)	Week 24 (n=61)	Week 48 (n=61)	Week 96 (n=59)*
Low	9 (15%)	52 (85%)	55 (90%)	59 (100%)
Moderate	30 (49%)	9 (15%)	6 (10%)	0 (0%)
High	22 (36%)	0 (0%)	0 (0%)	0 (0%)

Teriflunomide Treatment Arm

DA Score Category	Baseline (n=20)	Week 24 (n=20)	Week 48 (n=20)	Week 96 (n=20)
Low	4 (20%)	4 (20%)	2 (10%)	6 (30%)
Moderate	13 (65%)	11 (55%)	15 (75%)	9 (45%)
High	3 (15%)	5 (25%)	3 (15%)	5 (25%)

*Two Week 96 samples were not available for analysis. For both participants, the DA categorization at the available preceding timepoint were in the Low category

Table 2: Overall Disease Activity Score Categorization by Timepoint and Treatment Arm

Results

- Statistically significant average treatment effects, holding baseline value, sex, and age constant, were observed for the overall DA Score and each of the 4 Disease Pathway Scores, resulting in lower scores for the ublituximab arm compared to the teriflunomide arm ($p<0.05$; Bonferroni corrected). (Figure 1)
- Statistically significant average treatment effects, holding baseline value, sex, and age constant, were observed for 10 of the 18 individual biomarkers: NEFL, MOG, CXCL13, OPG, TNFRSF10A, PRTG, FLRT2, TNFSF13B, OPN, and GFAP ($p<0.05$; Bonferroni corrected). (Figure 2)
- For the 61 participants treated with ublituximab; at baseline, 15% had Low DA, 49% had Moderate DA and 36% had High DA Scores. At Week 96, 100% of the ublituximab participants had Low DA Scores. For the 20 participants treated with teriflunomide; at baseline, 20% had Low DA, 65% had Moderate DA and 15% had High DA Scores. At Week 96, 30% of the teriflunomide participants had Low DA, 45% had Moderate DA and 25% had High DA Scores. (Table 2)
- Classification performance relative to the disease activity endpoints used to validate the MSDA test was evaluated in each treatment arm using the area under the receiver operating characteristic curve (AUROC). 95% Confidence intervals for the AUROC for classification of Gd+ lesions, N/E T2 lesions, and active/stable status in both treatment arms either were better or overlapping with those observed in the MSDA clinical validation study.

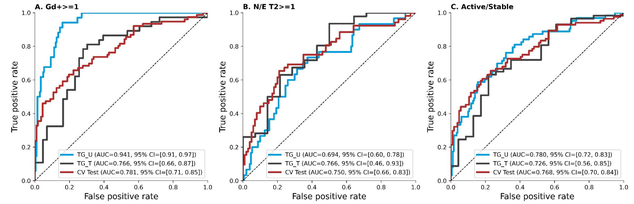

Figure 3: AUROC and 95%CIs for the Gd+, New T2, and Active/Stable endpoints for TG ULTIMATE, by treatment arm compared to the MSDA clinical validation study

Conclusions

- Ublituximab treatment over 96 weeks resulted in significant average treatment effects versus the teriflunomide arm for the overall Disease Activity Score and each of the 4 Disease Pathway Scores (all scores decrease for the ublituximab arm), and 10 individual biomarkers over the duration of the study.
- Comparable classification performance for both treatment arms in this study was observed for the radiographic and clinical endpoints used to validate the MSDA test.
- These results suggest that the MSDA test can serve as a quantitative measurement tool for evaluation of disease activity and therapeutic efficacy.

Disclosures: Ferhan Qureshi, Shannon McCurdy, Elisa Sheng, Wayne Hu, Alexander Hari, and Srushti Tiwari are employees of Octave Bioscience. Ati Ghoreyshi is a former employee of Octave Bioscience. Christopher Garner and Hari Miskin are employees of TG Therapeutics. John Foley has received research support from Biogen, Imstem, Octave, Innodem and TG Therapeutics. He received speakers' honoraria and/or acted as a consultant for Biogen, Horizon, Sandos and TG Therapeutics. He has equity interest in Octave. He is the founder of InterPro Biosciences.

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