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Disease Activity Score and Disease Pathway Scores Measured Using the Multiple Sclerosis Disease Activity Test are Significantly Reduced Prior to the Week 96 Dose for Patients Treated with Ublituximab in the Phase 3 ULTIMATE I and II Studies

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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 [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 overall DA Score, 4 Pathway Scores (Immunomodulation, Neuroinflammation, Myelin Biology and Neuroaxonal Integrity) and 18 individual proteins in 21 patients treated with ublituximab across 4 timepoints: (1) Week 0 = sample drawn prior to the first 150 mg Infusion (2) Week 24 = sample drawn pre-dose prior to a 450 mg infusion (3) Week 48 = sample drawn pre-dose prior to a 450 mg infusion (4) Week 96 = sample drawn pre-dose prior to a 450 mg infusion. 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.

Methods

82 serum samples from 21 ULTIMATE study participants were assayed using the MSDA Test and evaluated for change over time. Up to 4 longitudinal timepoints were analyzed per patient: Week 0, Week 24, Week 48, and Week 96. For two of the 21 patients the Week 96 sample was not available. All blood draws were performed prior to the ublituximab dose administration associated with each of the timepoints. To evaluate the significance of the trends observed across the 4 timepoints, the average change per week in individual proteins, DA score and each of the 4 Pathway Scores was estimated from a mixed effects model of the biomarker endpoint on weeks from baseline with random intercepts corresponding to the study participant. 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 analyzed at each timepoint were categorized accordingly and compared across timepoints. Area Under the receiver operating Curve (AUC) analysis was performed for the DA score model to evaluate correlation with endpoints that were evaluated in a previous study to clinically validate the MSDA algorithm including: the presence of T1 gadolinium (Gd+) lesions, the presence of new or enlarging (N/E) T2 lesions, and active/stable status (defined as a composite binary variable that combined any radiographic and/or clinical evidence of disease activity including clinical relapse, Gd+ and N/E T2 lesions).

TG Summary Table					
Characteristic	**0,** N = 21[1]	**24,** N = 21[1]	**48,** N = 21[1]	**96,** N = 19[1]	**p-value**[2]
Sex (male)	7 (33%)	7 (33%)	7 (33%)	7 (37%)	>0.9
Age	40 (37. 48)	40 (37. 48)	41 (38. 49)	42 (38, 49)	>0.9
GD+ >= 1	9 (43%)	0 (0%)	1 (4.8%)	0 (0%)	<0.001
Unknown	0	1	0	0	
Relapse count					<0.001
0	1 (4.8%)	18 (86%)	18 (86%)	17 (89%)	
1	14 (67%)	2 (9.5%)	2 (9.5%)	1 (5.3%)	
2	6 (29%)	1 (4.8%)	1 (4.8%)	1 (5.3%)	
NE T2 >= 1					<0.001
0	0 (0%)	15 (71%)	19 (90%)	19 (100%)	
1+	0 (0%)	5 (24%)	2 (9.5%)	0 (0%)	
Unknown	21 (100%)	1 (4.8%)	0 (0%)	0 (0%)	
Active/Stable	20 (95%)	7 (33%)	5 (24%)	2 (11%)	<0.001

[1] n (%): Median (IOR) [2] Pearson's Chi-squared test; Kruskal-Wallis rank sum test; Fisher's exact test

Table 1: Demographic Information, grouped by timepoint (weeks).

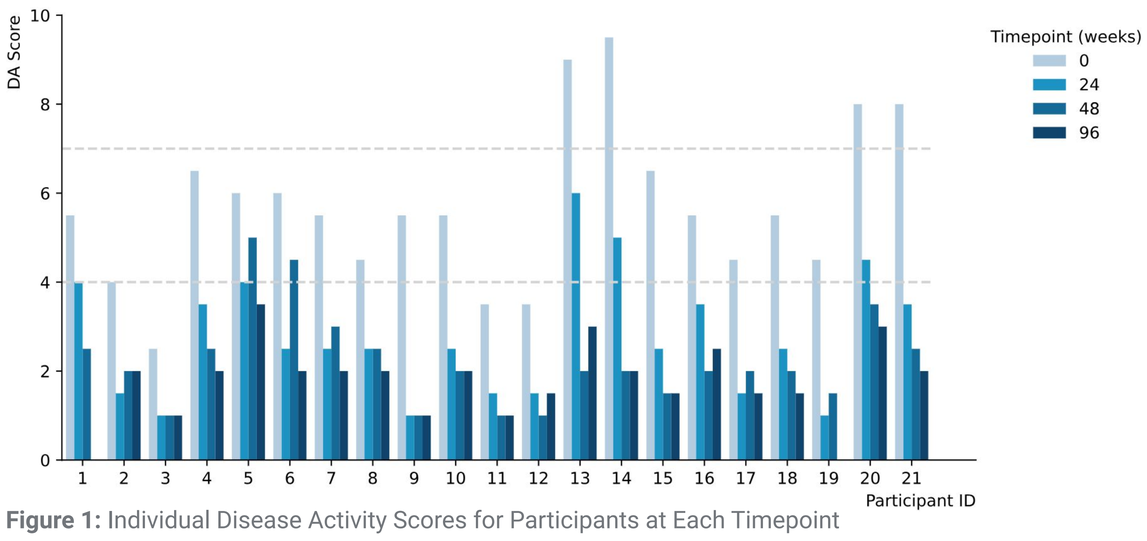


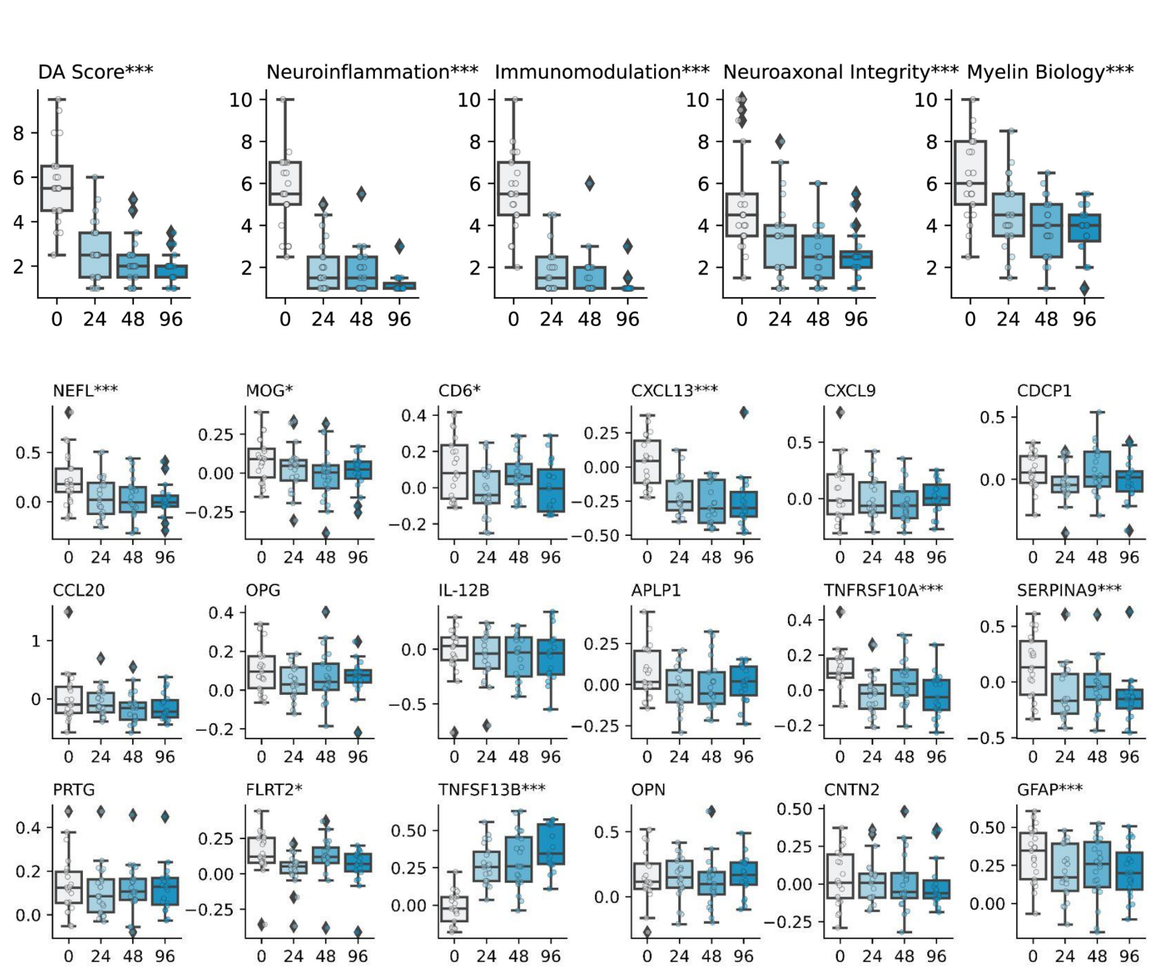
Figure 1: Individual Disease Activity Scores for Participants at Each Timepoint

Results

- Statistically significant decreases (p<0.05; Bonferroni corrected) were observed for the overall Disease Activity Score and each of the 4 Disease Pathway Scores across all timepoints.
- Statistically significant trends (p<0.05; Bonferroni corrected) were observed for 6 of the 18 individual biomarkers across all timepoints: NfL, CXCL13, TNFRSF10A, SERPINA9, TNFSF13B and GFAP.
- Based on the overall DA score categorization at baseline, of the 21 participants: 5 had Low Disease Activity, 12 had Moderate Disease Activity and 4 had High Disease Activity. Each of the 21 patients had Low Disease Activity at the final timepoint for which they were assessed in this cohort.
- The MSDA algorithm was highly correlated with decreasing disease activity, measured by Gd+ lesions, N/E T2 lesions and active/stable status. The Area Under the Receiver Operating Characteristic Curve (AUROC) for each of the aforementioned endpoints was determined to be 0.88, 0.84 and 0.84 respectively.

DA Score Category	Baseline (n=21)	Week 24 (n=21)	Week 48 (n=21)	Week 96 (n=19)*
Low	5 (24%)	18 (86%)	19 (90%)	19 (100%)
Moderate	12 (57%)	3 (14%)	2 (10%)	0 (0%)
High	4 (19%)	0 (0%)	0 (0%)	0 (0%)

Table 2: Overall Disease Activity Score Categorization by Timepoint: n (%)



*p <0.05, *** p <0.05 Bonferroni corrected

Figure 2: Box and whisker plots of (A) Disease Activity Score and 4 Disease Pathway Scores and (B) 18 individual proteins measured in the MSDA test

Conclusions

- Ublituximab treatment over 96 weeks resulted in significant decreases for the overall Disease Activity Score, and each of the 4 Disease Pathway Scores. 6 individual biomarkers had significant trends across the 4 timepoints including 3 proteins well established as being associated with B-cell biology (CXCL13, SERPINA9 and TNFSF13B (BAFF)).
- Excellent classification performance from the MSDA test was observed for the radiographic and clinical disease activity endpoints evaluated in this cohort.
- 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, Anisha Keshavan, Shannon McCurdy and Ati Ghoreyshi are employees of Octave Bioscience. Denise Campagnolo, Lily Lee, and Teja Turpuseema are employees of TG Therapeutics.John Foley has received research support from Biogen, Novartis, Imstem, Octave Bioscience, TG Therapeutics and Genentech. He received speakers' honoraria and/or acted as a consultant for Biogen, and TG Therapeutics. He is the founder of InterPro Biosciences

References: [1] Steinman, L, Fox E, Hartung H et al. Ublituximab versus Teriflunomide in Relapsing Multiple Sclerosis. N Engl J Med. Aug 2022. DOI: 10.1056/NEJMoa2201904 [2] Qureshi F, Hu W, Loh L, et al. Analytical validation of a multi-protein, serum-based assay for disease activity assessments in multiple sclerosis. Proteomics Clinical Applications. Feb 2023. https://doi.org/10.1002/prca.202200018 [3] Chitnis T, Foley J, Ionete C, et al. Clinical Validation of a Multi-protein, Serum-based Assay for Disease Activity Assessments in Multiple Sclerosis. Clinical Immunology. Aug 2023. https://doi.org/10.1016/j.clim.2023.109688