A Multi-Protein Disease Activity Score Mediates N/E T2 Lesion Reduction by Ublituximab vs. Teriflunomide in Relapsing MS

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P1384

Introduction

Ublituximab is a glycoengineered anti-CD20 monoclonal antibody for relapsing multiple sclerosis (RMS) [1]. The Multiple Sclerosis Disease Activity (MSDA) Test is a validated, multi-protein assay that generates a Disease Activity (DA) Score (range 1-10) from 18 biomarkers, sex, and age [2, 3]. Previous data demonstrated that ublituximab significantly lowered the overall DA score versus teriflunomide [4].

Objectives

To estimate the DA score association with MRI and clinical outcomes and mediation of ublituximab (UB) versus teriflunomide (TER) efficacy in participants with RMS.

Methods

- **Study Design:** Post-hoc analysis of Phase 3 ULTIMATE I/II trials (Baseline to 96 weeks) [6].
- **Cohort:** N=81 participants (UB N=61; TER N=20) contributing 322 paired serum and MRI measurements, along with treated and confirmed relapse records.
- **Statistical Analysis:**
  - **DA score associations with MRI and clinical endpoints:**
    - Baseline gadolinium-enhancing (Gd+) lesion associations with the DA score were assessed via logistic regression, adjusted for age, sex, and treatment group.
    - Post-baseline Gd+ (TER only, secondary) and new/enlarging (N/E) T2 lesion associations were evaluated using generalized linear mixed-effects models (GLMMs). Both models were adjusted for age, sex, and baseline DA score; the N/E T2 model was also adjusted for treatment group.
    - Associations with relapse were assessed via an Andersen-Gill recurrent events model with a time-varying DA score. Covariate adjustments were explored in sensitivity analyses.
    - Significance was Bonferroni-corrected (alpha=0.05, N_B=3).
  - **DA score mediation of the treatment effect on N/E T2 lesions:**
    - A multilevel 2-1-1 causal mediation analysis evaluated DA score mediation of the treatment effect on N/E T2 lesions, pairing an adjusted linear mixed mediator model with an adjusted logistic GLMM outcome model.

Table 1: Characteristics of ULTIMATE I/II participants (N=81, 322 samples) by treatment and timepoint. "Relapse count" denotes the number of participants with treated, IRAP-confirmed relapses within the preceding visit window (e.g., Baseline to 24W). (DA = Disease Activity; Gd+ = Gadolinium-enhancing; IRAP = Independent Relapse Adjudication Panel; N/E T2 = New/Enlarging T2)

Statistic	Value	Grouped by Timepoint and Treatment Group			
		Ublituximab Group			
		Baseline	24W	48W	96W
n		61	61	61	59
Sex, n (%)	Female	38 (62.3)	38 (62.3)	38 (62.3)	36 (61.0)
	Male	23 (37.7)	23 (37.7)	23 (37.7)	23 (39.0)
Age (years), mean (SD)		38.6 (8.9)	39.1 (8.9)	39.5 (8.9)	40.1 (8.8)
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)		
N/E T2 >= 1, n (%)	0		33 (54.1)	59 (96.7)	58 (98.3)
	1+		27 (44.3)	2 (3.3)	1 (1.7)
	Unknown		1 (1.6)		
Relapse count by end of interval, n (%)	0		56 (91.8)	60 (98.4)	57 (93.4)
	1		5 (8.2)	1 (1.6)	3 (4.9)
	2				1 (1.6)
DA score, mean (SD)		6.5 (2.0)	2.7 (1.3)	2.2 (1.2)	1.9 (0.8)
		Teriflunomide Group			
		Baseline	24W	48W	96W
n		20	20	20	20
Sex, n (%)	Female	14 (70.0)	14 (70.0)	14 (70.0)	14 (70.0)
	Male	6 (30.0)	6 (30.0)	6 (30.0)	6 (30.0)
Age (years), mean (SD)		34.7 (11.4)	35.2 (11.4)	35.7 (11.4)	36.6 (11.4)
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				
N/E T2 >= 1, n (%)	0		6 (30.0)	4 (20.0)	4 (20.0)
	1+		14 (70.0)	16 (80.0)	16 (80.0)
	Unknown				
Relapse count by end of interval, n (%)	0		16 (80.0)	18 (90.0)	16 (80.0)
	1		4 (20.0)	2 (10.0)	4 (20.0)
	2				
DA score, mean (SD)		5.6 (1.9)	5.8 (1.8)	5.8 (1.5)	5.5 (2.0)

Disclosure: S. McCurdy, E. Toy, G. Datta, J. Verrier, W. Hu, D. Brazel, and T. Livingston are employees of and have an equity interest in Octave Bioscience. F. Qureshi is a former employee of and has an equity interest in Octave Bioscience. C. Rowland, C. Garner, and H. Miskin are employees of and have an equity interest in TG Therapeutics. J. 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.

References:[1] Foley JF et al. Ublituximab demonstrates enhanced ADCC. AAN 2023. [2] Qureshi F et al. Analytical validation of a multi-protein assay. Proteomics Clin Appl. 2023. [3] Chitnis T et al. Clinical validation of a multi-protein assay. Clin Immunol. 2023. [4] Qureshi F et al. Comparison of MSDA results in ULTIMATE I/II. ECTRIMS 2024. [5] Qureshi F et al. MSDA Test Reveals Distinct Trajectories in ULTIMATE I/II. ACTRIMS 2025. [6] Steinman L et al. Ublituximab vs teriflunomide in relapsing MS. N Engl J Med. 2022.

Results

- **The DA score is associated with MRI lesions:** Each 1-point increase in the DA score was associated with a **43% (95%CI=[1.11, 1.86], p_B=0.019)** increase in the odds of having Gd+ lesions at baseline, and a **59% (95%CI=[1.13, 2.23], p_B=0.022)** increase in the odds of developing N/E T2 lesions post-baseline. For the secondary post-baseline Gd+ analysis (TER only), each 1 point-increase in the DA score was associated with a **2.24-fold (95%CI=[1.24, 4.05]; p=0.008)** increase in the adjusted odds of having Gd+ lesions. DA score associations with relapse were not significant after Bonferroni correction.
- **The DA score mediates a significant treatment effect on N/E T2 lesions:** Ublituximab significantly reduced the probability of N/E T2 lesions overall (**Total Effect =-0.596, 95%CI=[-0.733, -0.433], p<0.001**), and **45.5%** of that benefit was attributable to treatment-related changes in the DA score (**Average Proportion Mediated, 95%CI=[0.116, 0.820], p=0.014**).

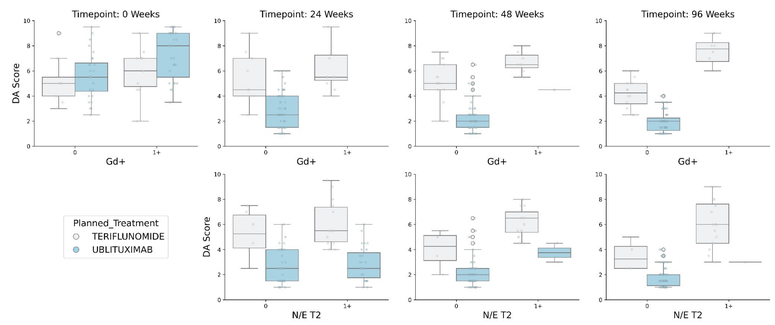


Figure 1: Distribution of DA scores stratified by lesion status and treatment group. Scores are stratified by the presence or absence of Gd+ (top) and N/E T2 lesions (bottom) at each timepoint. Boxplots show median and IQR; circles represent individual data points and outliers. (DA = Disease Activity; Gd+ = Gadolinium-enhancing; N/E T2 = New/Enlarging T2)

Conclusions

These results support the use of the DA score as a clinically validated surrogate for MRI disease activity. The finding that the DA score mediates nearly 50% of ublituximab's effect on N/E T2 lesion activity suggests that the DA score captures critical components of the biological treatment response and supports its validity in clinical practice to monitor treatment response and identify patients at higher risk for subclinical disease activity.

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