Multivariate Proteomic MS Disease Activity Test Result Distributions Based on Disease Modifying Therapy Categories

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Background

A custom immunoassay panel that measures the concentrations of 18 proteins to determine 4 disease pathway scores and an overall disease activity score was analytically validated (Hu et al., 2021) and clinically validated (Chitnis et al., 2021) based on associations with clinical and radiographic disease activity endpoints. In the MS Disease Activity (MSDA)Test we used Gd lesions as the primary endpoint to estimate the disease activity and pathways scores; other endpoints such as new/enlarging T2 lesions and active/stable status were evaluated as well. Patients with MS are treated with a variety of disease modifying therapies (DMT) that have diverse mechanisms of action (MOA) impacting their efficacy. A disease activity measurement tool should reflect therapeutic efficacy and should be characterized relative to the biological impact of various MOAs.

Objective

To assess the effect of DMT class MOA relative to the individual biomarkers and algorithmic scores reported from a proteomic MSDA Test.

Cohort

Serum samples were obtained from 4 sites - Brigham and Women's Hospital (BWH -CLIMB Study), University of Massachusetts (UMASS -FSDD Study), American University of Beirut (AUB) and the Rocky Mountain Multiple Sclerosis Clinic (RMMSC) to perform a clinical validation study for the MSDA test. 502 serum samples from this study were categorized based on 6 different DMT categories reflecting the therapy the patient was on at the time of the blood draw: Interferons (Interferon beta 1a, Peginterferon beta 1a, Interferon beta 1b), Fingolimod, Dimethyl Fumarate, Glatiramer Acetate, Natalizumab, and anti-CD20s (Ocrelizumab, Rituximab).

Table 1: Summary table for demographic data for the whole cohort, categorized by DMT treatment group at the time of blood draw, study site and number of Gd+ lesions.

		N	%
Sample Size		502	100
DMT Class			
	Anti-CD20	41	8.2
	Natalizumab	130	25.9
	Interferons	94	18.7
	Dimethyl Fumarate	64	12.7
	Fingolimod	77	15.3
	Glatiramer Acetate	63	12.5
	Other (excluded)	33	6.6
Gd+ Status			
	0 Lesions	349	69.5
	1 Lesion	112	22.3
	≥ 2 Lesions	41	8.2
Site			
	AUB	175	34.9
	BWH	152	30.3
	RMMSC	157	31.3
	UMASS	18	3.60
Age (Mean ± SD)		42.22 ± 13.0	
Disease Duration (Mean ± SD)		9.68 ± 8.0	
Sex			
	Female	355	70.7
	Male	147	29.3

Analysis

- Distribution of each protein biomarker measured in the MSDA Test assay panel (Chitnis et al., 2021) - GH and VCAN are not part of the MSDA Test assay panel; protein concentration values have been corrected for age and sex- for the 6 different DMT treatment categories; the ANOVA p-values show that there are significant differences among DMT categories for 17 of the 20 biomarkers (Fig. 1).
- We analyzed the distribution of the disease activity and disease pathway scores obtained from the MSDA Test for each DMT category as described in Chitnis et al. 2021 (also poster P018 ACTRIMS 2022) - see Fig. 2. Table 2 summarizes the differences among DMT classes.

Table 2: Mean and median disease activity (DA) and pathway scores categorized by DMT treatment.

DMT Class	DA Score		Neuroinflammation		Immunomodulation		Neuroaxonal Integrity		Myelin Biology	
	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median
Anti-CD20	3.23 ± 1.86	2.5	2.70 ± 2.19	1.5	2.55 ± 2.08	1.5	3.82 ± 2.04	3.5	4.24 ± 1.49	4
Natalizumab	4.13 ± 1.72	3.5	3.87 ± 2.04	3.5	3.57 ± 1.89	3	4.09 ± 2.05	4	5.00 ± 1.55	5
Interferons	4.44 ± 2.22	4	4.22 ± 2.41	3.75	3.71 ± 2.20	3	4.52 ± 2.70	3.75	5.24 ± 1.92	5
Dimethyl Fumarate	4.63 ± 1.90	4.5	5.00 ± 2.13	4.75	4.52 ± 2.02	4	4.34 ± 2.27	4	4.77 ± 1.72	4.5
Fingolimod	4.73 ± 1.67	4.5	4.82 ± 1.95	4.5	4.34 ± 1.87	4	4.36 ± 2.07	4.5	5.42 ± 1.53	5
Glatiramer Acetate	6.15 ± 1.88	6	6.47 ± 2.28	6.5	6.04 ± 2.15	6	5.72 ± 2.27	6	6.37 ± 1.52	6.5

- Splitting the dataset by the Gd Lesion count (0, 1, 2+), we also analyzed trends for the disease duration among the radiographic evidence groups (see Table 3).

Results

- Higher concentrations of TNFSF13B and VCAN and lower concentration of SERPINA9 were observed in the Anti-CD20 category relative to the other DMT groups; the Glatiramer Acetate group has higher concentration of CXCL9, and lower concentration of TNFSF13B relative to the other DMT groups; the Fingolimod Hydrochloride group shows lower concentration of IL-12B and CD6. Clear variations across DMTs were observed in the mean, median and 95% confidence intervals for GH, CXCL13, CCL20 (see Fig. 1).
- Lower DA scores were observed in patients without radiographic evidence of disease activity (0 Gd lesions) for all DMT categories (see Table 2).
- A comparison of the DA score between the different DMT categories (Table 2) shows that the 41 patient samples from the anti-CD20 category have the lowest DA score on average (3.23 ± 1.86), followed by the 130 patient samples from the Natalizumab category (4.13 ± 1.72). The highest DA score on average is associated with the 63 patients taking Glatiramer Acetate (6.15 ± 1.88).

Fig. 1: Protein biomarker distribution, split by DMT class. Significant ANOVA Bonferroni corrected p-values, based on biomarkers across DMTs, are marked in red.

Fig 2: Distribution of the disease activity and pathway scores categorized by DMT treatment. Score scales range from 1.0 to 10.0 with 0.5 intervals. Scores have been color-coded based on validated disease activity thresholds: Low (0 Gd lesions), Medium (1 Gd lesion) and High (2+ Gd lesions)

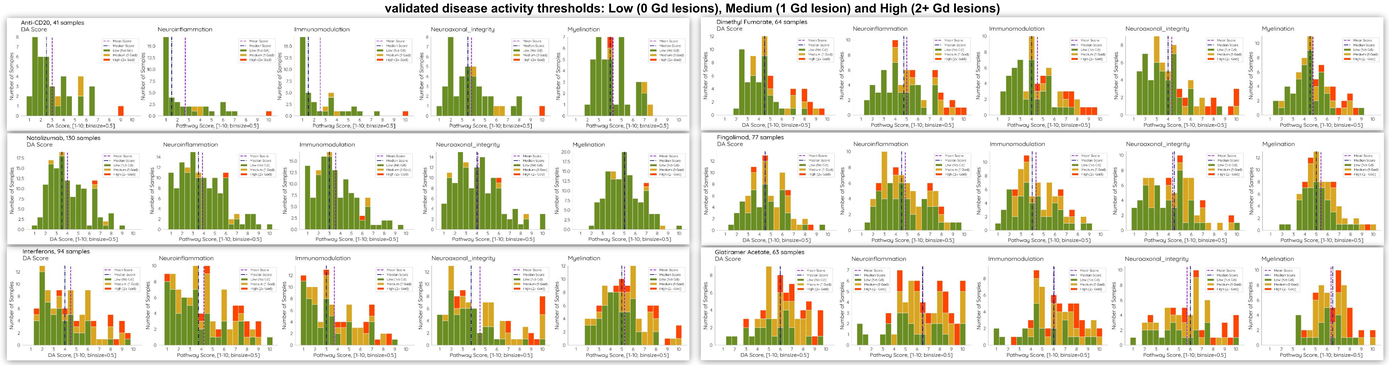

Table 3: Number of samples by DMT class and Gd Lesions and the mean ± SD of the DA and pathways scores.

DMT Class	Gd lesion count	# Samples	Disease duration	DA Score	Neuroinflammation	Immunomodulation	Neuroaxonal Integrity	Myelin Biology
Anti-CD20	0	37	6.37 ± 3.99	2.95 ± 1.59	2.41 ± 1.91	2.27 ± 1.76	3.51 ± 1.77	4.09 ± 1.39
	1	3	1.66 ± 1.65	4.83 ± 1.15	3.83 ± 0.29	3.50 ± 0.50	5.50 ± 1.32	6.17 ± 1.89
	2+	1	16.9	9	10	10	10	4
Dimethyl Fumarate	0	44	9.54 ± 8.40	3.88 ± 1.29	4.23 ± 1.70	3.73 ± 1.55	3.43 ± 1.50	4.24 ± 1.43
	1	12	8.17 ± 5.47	5.54 ± 1.89	6.00 ± 1.73	5.54 ± 1.62	5.25 ± 2.16	5.38 ± 1.87
	2+	8	5.09 ± 5.67	7.44 ± 1.66	7.75 ± 2.05	7.31 ± 1.79	7.94 ± 1.92	6.81 ± 1.19
Fingolimod	0	48	8.30 ± 6.60	4.36 ± 1.65	4.65 ±1.98	4.10 ± 1.91	3.74 ± 1.87	5.01 ± 1.31
	1	25	8.87 ± 8.83	4.83 ± 1.15	3.83 ± 0.29	3.50 ± 0.50	5.50 ± 1.32	6.17 ± 1.89
	2+	4	4.69 ± 3.38	5.75 ± 2.22	5.38 ± 2.56	5.00 ± 2.38	6.38 ± 2.43	6.12 ± 2.50
Glatiramer Acetate	0	23	12.37 ± 10.80	5.24 ± 1.96	5.43 ± 2.57	5.09 ± 2.34	4.70 ± 2.20	5.76 ± 1.48
	1	27	9.14 ± 8.66	6.41 ± 1.37	6.94 ± 1.77	6.52 ± 1.72	5.76 ± 1.72	6.46 ± 1.34
	2+	13	8.12 ± 6.92	7.23 ± 2.04	7.31 ± 2.16	6.73 ± 2.14	7.46 ± 2.43	7.23 ± 1.58
Interferons	0	53	7.24 ± 6.29	3.48 ± 1.70	3.33 ± 2.14	2.85 ± 1.90	3.32 ± 1.85	4.49 ± 1.40
	1	30	9.82 ± 7.63	5.33 ± 1.98	5.00 ± 2.11	4.45 ± 1.87	5.65 ± 2.68	5.98 ± 1.95
	2+	11	5.53 ± 5.48	6.59 ± 2.69	6.41 ± 2.45	5.82 ± 2.39	7.23 ± 3.12	6.86 ± 2.38
Natalizumab	0	125	13.13 ± 10.13	4.08 ± 1.70	3.82 ± 2.03	3.52 ± 1.87	4.06 ± 2.02	4.95 ± 1.52
	1	4	12.45 ± 5.28	5.00 ± 2.38	4.88 ± 2.21	4.50 ± 2.35	4.75 ± 3.12	5.88 ± 2.25
	2+	1	2.2	6.5	6	6	6	7

Results (cont.)

- When evaluating the Gd Lesion count across all DMT categories (Table 3), we observe an overall increase of the disease activity and pathway scores as the number of Gd lesions increases.
- In general, higher Gd lesions are associated with patients with fewer years since the diagnosis, however this finding may be a result of newly diagnosed patients not being administered higher efficacy DMTs.

Conclusions

- We find that the samples associated with the lowest disease activity scores are from the anti-CD20 category, followed by Natalizumab, which represent the highest efficacy treatments in our categorizations.
- The DA and disease pathways scores are inversely correlated with disease duration for 4 out of 6 DMT groups - except Interferons and Dimethyl Fumarate DMT groups: higher Gd lesions are associated with patients with fewer years since diagnosis.
- There is a direct correlation between DA and disease pathways scores with Gd lesions across all DMT groups: as the DA and pathway scores increase, the number of Gd lesions increases as well.
- Overall, lower DA scores were observed in patients without radiographic evidence of disease activity (0 Gd lesions) for all DMT categories.
- We plan to expand the analysis with additional studies and factoring in other endpoints, including duration on the DMT, previous DMT history, and the impact of DMT mechanism of action on individual biomarker concentrations.

References

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