Association of Mycophenolate and Azathioprine Use with Cognitive Dysfunction in Systemic Lupus

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Background

- Cognitive dysfunction (CD) is a common manifestation of systemic lupus erythematosus (SLE) , affecting an estimated 40% of patients.
- To date, no treatments have been approved for SLE-CD.
- An important mechanism implicated in SLE-CD is microglial activation.
- Azathioprine (AZA) and mycophenolate (MMF) have been shown in prior studies to inhibit microglial activation and are not known to cause neurotoxicity.
- Given these qualities, we hypothesize that use of AZA or MMF could be associated with reduced odds of SLE-CD.

Specific Aim

To assess the association of AZA and MMF use with SLE-CD.

Methods

Design: Longitudinal study which analyzed prospectively collected data. Measurements were completed at 0, 6 and 12 months.

Participants: All consenting adult SLE patients attending the University of Toronto / University Health Network Lupus Clinic from 2016 to 2020.

Procedures: A neuropsychological battery (NB) was administered and clinical and demographic data were gathered at each visit. NB scores were compared to normative, standardized scores.

Covariates:

- SLE Disease Activity Index-2000 Glucocorticoid & SLE Damage Index scores.
- Additional CD risk factors: hypertension, obesity, and/or active smoker.
- Persistent antiphospholipid antibody positivity; History of lupus nephritis
- Active use of an additional immunomodulator: antimalarials, belimumab, calcineurin inhibitor, cyclophosphamide, methotrexate, rituximab; Prior use of AZA, calcineurin inhibitor, cyclophosphamide, methotrexate, MMF.
- Beck Depression Inventory & Beck Anxiety Inventory scores.
- Age; Sex; Ethnicity (Black, Caucasian, Chinese or other).
- Education level (completion of a College or University degree versus not).
- Employment status (employed or full time student versus not).
- Marital status (married or common-law partner versus not).

Methods

Outcomes: Primary Outcome: Cognitive dysfunction (CD), defined as a z-score of ≤-1.5 in ≥2 cognitive domains on the NB. Secondary Outcome: Non-CD, defined as no z-score ≤-1.5.

Predictors: Primary: (1) cumulative AZA dose, (2) cumulative MMF dose (g/kg), Secondary: (1) active AZA use, (2) active MMF use (≥6 months); (3) duration of MMF, (4) duration of AZA use (years).

Statistical analysis: Mixed-effects logistic regression models were constructed to estimate the odds of CD and non-CD with respect to AZA and MMF use over the three follow-up periods.

Results

Table 1. Baseline characteristics of participants by cognitive function

	Total n=300	Non-CD n=143 (47.7%)	CD n=157 (52.3%)	Absolute Standardized Differences (%)	p-values
Sex, n (%)					
Female	267 (89.0%)	129 (90.2%)	138 (87.9%)	0.1%	0.52
Male	33 (11.0%)	14 (9.8%)	19 (12.1%)		
Age in years, mean ± SD	41.1 ± 12.1	41.4 ± 11.6	40.8 ± 12.5	6.4%	0.53
Ethnicity					
Black	59 (19.7%)	19 (13.3%)	40 (25.5%)	**31.1%**	**0.01**
White	162 (54.2%)	93 (65.0%)	69 (43.9%)	**43.2%**	**<0.01**
Chinese	33 (11.0%)	10 (7.0%)	23 (14.7%)	**24.8%**	**0.03**
Others	46 (15.3%)	21 (14.7%)	25 (15.9%)	3.4%	0.77
Education Level, highest achieved, n (%)					
12th Grade or lower	60 (20.0%)	22 (15.4%)	38 (24.2%)		
College or University Degree	240 (80.0%)	121 (84.6%)	119 (75.8%)	**28.6%**	0.06
Employment Status, n (%)					
Employed or student	195 (65.0%)	100 (69.9%)	95 (60.5%)	**30.9%**	0.09
Other	105 (35.0%)	43 (30.1%)	62 (39.5%)		
Marital Status, n (%)					
Married or common Law	119 (39.9%)	66 (46.2%)	53 (33.8%)	**32.0%**	**0.04**
Other	179 (60.0%)	77 (53.8%)	102 (65.0%)		
SLE Manifestations, n (%)					
Antiphospholipid positivity	46 (15.3%)	25 (17.5%)	21 (13.4%)	**15.8**	0.32
Nephritis	91 (30.3%)	42 (29.4%)	49 (31.2%)	1.2%	0.97
Mucocutaneous	172 (57.5%)	85 (59.9%)	87 (55.4%)	**13.2%**	0.44
Musculoskeletal	112 (37.5%)	49 (34.5%)	63 (40.1%)	7.2%	0.32
Other NPSLE manifestation	75 (25.0%)	31 (21.7%)	44 (28.0%)	3.8%	0.21
Serositis	26 (8.7%)	16 (11.3%)	10 (6.4%)	3.4%	0.13
Additional CD risk factors, n (%)					
Hypertension	124 (41.3%)	63 (44.1%)	61 (38.9%)	10.1%	0.36
Obesity	97 (32.3%)	44 (30.8%)	53 (33.8%)	**14.7%**	0.58
Smoker	18 (6.0%)	8 (5.6%)	10 (6.4%)	2.0%	0.78
Disease Duration in years, median (IQR)	12.4 (6.0, 21.6)	13.4 (6.4, 22.7)	12.0 (5.5, 19.7)	**15.5%**	0.20
SDI score					
Median (IQR)	1.0 (0.0-2.0)	0.0 (0.0-2.0)	1.0 (0.0-2.0)	10.3%	
Mean ± SD	1.05 ± 1.45	1.00 ± 1.41	1.09 ± 1.49		0.52
SLEDAI-2K score					
Median (IQR)	2.0 (0.0, 4.0)	2.0 (0.0, 4.0)	2.0 (0.0, 4.0)		
Mean ± SD	3.3 ± 3.8	3.1 ± 3.4	3.4 ± 4.1	4.2%	0.87
SLEDAI-2G score					
Median (IQR)	3.1 (0.9-6.2)	3.0 (0.93-6.1)	3.2 (0.8-6.2)	7.1%	
Mean ± SD	4.4 ± 4.7	4.1 ± 4.4	4.6 ± 5.0		0.77
Glucocorticoid dose, mg/day					
Mean ± SD	4.3 ± 8.1	4.2 ± 7.7	4.5 ± 8.4	9.2%	0.84
Immunosuppressant use, n (%)					
Antimalarials	224 (82.4%)	109 (82.6%)	115 (82.1%)	2.6%	0.93
Azathioprine	52 (17.3%)	32 (22.4%)	20 (12.7%)	**14.3%**	**0.03**
Belimumab	2 (0.7%)	1 (0.7%)	1 (6.4%)	10.2%	0.86
Cyclophosphamide	2 (0.7%)	2 (1.4%)	0 (0.0%)	10.8%	0.14
Cyclosporine	2 (0.7%)	1 (0.7%)	1 (6.4%)	7.5%	0.95
Glucocorticoids	132 (48.5%)	65 (49.2%)	67 (47.9%)	0.8%	0.82
Methotrexate	25 (8.8%)	10 (7.0%)	15 (9.6%)	5.5%	0.42
Mycophenolate	96 (32.0%)	41 (28.7%)	55 (35.0%)	3.5%	0.24
Rituxan	14 (4.7%)	7 (4.9%)	7 (4.5%)	2.6%	0.95
Prior Immunosuppressant Use, n (%)					
Azathioprine	2 (0.7%)	1 (0.7%)	1 (0.6%)	0.8%	0.95
Cyclophosphamide	0	0	0	-	-
Cyclosporine	0	0	0	-	-
Methotrexate	2 (0.7%)	0	2 (1.3%)	**16.1%**	0.18
Mycophenolate	23 (7.7%)	11 (7.7%)	12 (7.6%)	0.2%	0.99
Cumulative dose in g/kg, median (IQR)					
Azathioprine	2.29 (0.58, 4.89)	3.2 (1.0, 8.2)	1.9 (0.3, 3.1)	**28.0%**	**0.01**
Mycophenolate	37.6 (14.5, 78.6)	37.5 (14.2, 84.1)	43.5 (15.4, 88.9)	6.8%	0.22
Years of treatment, median (IQR)					
Azathioprine	4.9 (1.6, 12.0)	4.8 (1.5, 12.4)	3.0 (0.8, 5.5)	**57.8%**	0.21
Mycophenolate	4.5 (1.7, 8.6)	4.1 (1.1, 7.0)	4.4 (1.4, 8.4)	**18.2%**	0.41
Beck Depression Inventory score					
Median (IQR)	14.9 (7.2, 18.3)	13.4 (6.2, 16.4)	14.9 (8.3, 21.0)	**21.7%**	0.67
Beck Anxiety Inventory score					
Median (IQR)	15.6 (7.0, 20.0)	14.0 (6.0, 18.0)	15.6 (9.0, 21.0)	**21.6%**	0.39

Table 2. Characteristics of participants by AZA and MMF use

	No AZA use n=248	AZA use n=52	Absolute Standardized Differences	p-value	No MMF use n=204	MMF use n=96	Absolute Standardized Differences	p-value
SLICC-ACR Damage Index								
Median score (IQR)	1.0 (0.0, 1.0)	1.0 (0.0, 2.0)	**13.4%**	0.40	0.0 (0.0, 1.1)	1.0 (0.0, 2.0)	1.9%	0.32
Mean score ± SD	1.0 ± 1.4	1.2 ± 1.5			1.0 ± 1.5	1.1 ± 1.4		
Disease Duration in years, median (IQR)	12.7 (5.8, 21.9)	11.9 (6.7, 16.6)	**13.6%**	0.48	13.2 (6.0, 22.2)	11.6 (6.0, 19.4)	**19.4%**	0.22
SLEDAI-2K								
Median score (IQR)	2.0 (0.0, 4.0)	4.0 (2.0, 6.0)	**21.9%**	**<0.01**	2.0 (0.0, 4.0)	3.5 (0.0, 6.0)	**23.3%**	**0.03**
Mean score ± SD	3.1 ± 3.8	4.3 ± 3.6			2.9 ± 3.5	4.0 ± 4.2		
Other Immunosuppressant use, n (%)								
Antimalarials	183 (82.1%)	41 (83.7%)	4.3%	0.79	152 (82.6%)	72 (81.8%)	3.2%	0.87
Belimumab	11 (4.4%)	3 (5.8%)	**12.8%**	0.68	10 (4.9%)	4 (4.2%)	4.7%	0.78
Cyclophosphamide	2 (0.8%)	0	**11.9%**	0.52	2 (1.0%)	0	**13.4%**	0.33
Cyclosporine	2 (0.8%)	0	8.4%	0.52	2 (1.0%)	0	9.5%	0.33
Methotrexate	23 (9.3%)	2 (3.9%)	**21.2%**	0.20	23 (11.3%)	2 (2.1%)	**40.5%**	**0.01**
Rituximab	2 (0.8%)	0	**15.8%**	0.52	1 (0.5%)	1 (1.0%)	2.3%	0.58
Glucocticoid Dose, mg/day								
Mean ± SD	4.4 ± 8.5	4.2 ± 5.8	**12.3%**	0.23	3.1 ± 5.5	7.0 ± 11.4	**42.3%**	**<0.01**
SLE manifestations, n (%)								
Cognitive dysfunction	137 (55.2%)	20 (38.5%)	**19.8%**	**0.03**	102 (50.0%)	55 (57.3%)	3.7%	0.24
Antiphospholipid positivity	34 (13.7%)	12 (23.0%)	**21.5%**	0.09	28 (13.7%)	18 (18.8%)	**14.4%**	0.26
Nephritis	68 (27.5%)	25 (48.1%)	**37.0%**	**<0.01**	43 (21.1%)	50 (52.6%)	**64.6%**	**<0.01**
Mucocutaneous	137 (55.5%)	35 (67.3%)	5.8%	0.12	117 (57.4%)	55 (57.9%)	0.2%	0.93
Musculoskeletal	90 (36.4%)	22 (42.3%)	**12.1%**	0.43	76 (37.3%)	36 (37.9%)	2.6%	0.92
Other NPSLE manifestation	66 (26.6%)	9 (17.3%)	**31.8%**	0.16	50 (24.5%)	25 (26.0%)	3.9%	0.78
Serositis	20 (8.1%)	6 (11.5%)	5.1%	0.42	15 (7.4%)	11 (11.6%)	**25.0%**	0.23
Additional CD Risk Factors, n (%)								
Hypertension	100 (40.3%)	24 (46.2%)	**14.5%**	0.44	76 (37.3%)	48 (50.0%)	**21.1%**	**0.04**
Obesity	83 (33.5%)	14 (26.9%)	**23.3%**	0.36	63 (30.9%)	34 (35.4%)	10.4%	0.43
Smoker	14 (6.1%)	3 (5.8%)	**17.9%**	0.94	16 (7.8%)	2 (2.1%)	**20.1%**	**0.05**
Ethnicity								
Black	50 (20.2%)	9 (17.3%)	7.3%	0.64	36 (17.6%)	23 (24.0%)	**15.5%**	0.20
White	132 (53.2%)	30 (57.7%)	8.9%	0.56	111 (54.4%)	51 (53.1%)	2.6%	0.84
Chinese	27 (10.9%)	6 (11.5%)	2.1%	0.89	18 (8.8%)	15 (15.6%)	**20.8%**	0.08
Others	39 (15.7%)	7 (13.4%)	6.4%	0.68	39 (19.1%)	7 (7.3%)	**35.4%**	**0.01**
Education Level, highest achieved, n (%)								
12th Grade or lower	45 (18.1%)	15 (28.8%)			40 (19.6%)	20 (20.8%)		
College or University	203 (81.9%)	37 (71.2%)	**25.3%**	0.08	164 (80.4%)	76 (79.2%)	3.0%	0.80

Table 3. Mixed logistic regression results for azathioprine and mycophenolate use versus cognitive dysfunction[1]

	Cumulative dose, g/kg n=676		Use for ≥6 months n=676		Treatment duration, years n=676	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Azathioprine	**0.76 (0.61, 0.96)**	**0.02**	0.29 (0.08, 1.13)	0.07	**0.68 (0.50, 0.94)**	**0.02**
Mycophenolate	1.00 (0.99, 1.01)	0.44	0.83 (0.34, 2.05)	0.69	1.12 (0.96, 1.30)	0.15

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Summary

- 300 participants representing 676 patient visits completed the study. 157 (52%) met criteria for CD at baseline.
- There were no significant differences in mean age, glucocorticoid dose, disease duration, SLE Disease Activity Index-2000 (SLEDAI-2K) scores, or SLICC-ACR Damage Index (SDI) scores between CD and non-CD groups. .
- There were significantly more participants with CD who identified as Black or Chinese and significantly fewer participants identifying as White. There were also fewer married participants with CD.
- Participants taking AZA or MMF had significantly higher SLEDAI-2K scores and higher prevalence of nephritis; participants taking MMF had higher rates of hypertension, higher daily doses of glucocorticoid medications and lower rates of smoking.
- For each g/kg of cumulative AZA, there was on average a 24% reduced odds of CD: OR 0.76, 95% CI 0.61, 0.96, p=0.02.
- For each year of AZA treatment there was on average a 32% reduced odds of CD: OR 0.68 (0.50, 0.94), p=0.02.
- AZA use as binary variable (yes versus no) demonstrated a consistent trend toward reduced odds of CD with AZA use without reaching statistical significance: OR 0.29 (0.08, 1.12), p=0.07.
- MMF use was not associated with CD.
- MMF and AZA were not associated with the secondary outcome (non-CD.)

Conclusions

Despite higher disease activity scores in participants taking AZA compared to those not taking AZA, cumulative AZA dose and increasing AZA treatment duration were associated with significantly lower odds of SLE-CD.

MMF use was not associated with SLE-CD.