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Centrally acting ACE inhibitor (cACEi) and angiotensin receptor blocker (cARB) use and cognitive dysfunction in patients with SLE

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ABSTRACT

Objective Cognitive dysfunction (CD) is detectable in approximately 40% of patients with SLE. Despite this high prevalence, there are no approved pharmacological treatment options for this detrimental condition. Preliminary murine studies show potential for targeting microglial activation as a treatment of SLE-CD, which may be ameliorated with centrally acting ACE inhibitor (cACEi) and angiotensin receptor blocker (cARB) use. The aim of this study is to determine if there is an association of cACEi/cARB use with cognitive function in a human SLE cohort.

Methods The American College of Rheumatology neuropsychological battery was administered to patients with consecutive SLE at a single academic health centre at baseline, 6 and 12 months. Scores were compared with sex-matched and age-matched control subjects. Clinical and demographic data were gathered at each visit. The primary outcome was CD defined as dysfunction in two or more cognitive domains. The primary predictor was a total cumulative dose of cACEi/cARB in milligrams per kilogram, recorded as an equivalent ramipril dose. Odds of CD with respect to cACEi/cARB use were determined through generalised linear mixed modelling.

Results A total of 300 patients, representing 676 visits, completed this study. One hundred sixteen (39%) met the criteria for CD. Fifty-three participants (18%) were treated with a cACEi or cARB. Mean cumulative dose was 236 mg/kg (calculated as equivalent ramipril dose). Cumulative cACEi/cARB dose was not protective against SLE-CD. Caucasian ethnicity, current employment status and azathioprine cumulative dose were each associated with reduced odds of SLE-CD. Increasing Fatigue Severity Scale score was associated with increased odds of CD.

Conclusions In a single-centre SLE cohort, cACEi/cARB use was not associated with absence of CD. Many important confounders may have influenced the results of this retrospective study. A randomised trial is required to accurately determine if cACEi/cARB is a potential treatment for SLE-CD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cognitive dysfunction (CD) is a common neuropsychiatric manifestation of SLE and a major concern for patients, conferring an overall worse prognosis, lower rate of employment and poorer health-related quality of life. There are no approved treatments for SLE-CD, leaving an unacceptable gap in patient care.

⇒ Prior murine studies have shown that microglial activation is a potential therapeutic target for SLE-CD, which may be ameliorated by centrally acting ACE inhibitors (cACEi).

WHAT THIS STUDY ADDS

⇒ This is the first clinical study to examine the association between cACEi use and SLE-CD and did not reveal a statistically significant result. A randomised clinical trial is underway and is required to accurately determine if cACEi use is a potential treatment for SLE-CD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A greater understanding of the mechanisms involved in SLE-CD will help with developing future treatments.

INTRODUCTION

SLE is a chronic, multisystem autoimmune connective tissue disorder of unknown aetiology.[1 2] Nervous system involvement presenting as neurologic, psychiatric and cognitive disorders (CDs) occurs in approximately 50% of patients.[3] This spectrum of disorders is referred to as neuropsychiatric lupus (NPSLE) and includes 19 standardised central or peripheral nervous system conditions.[3 4] CD is an NPSLE syndrome stemming from diffuse central nervous system (CNS) pathology and has a variable prevalence of 15%–79% due to multiple challenges associated with obtaining an accurate diagnosis.[1 5–8] Diffuse, central NPSLE manifestations are more common than focal manifestations and have a significant effect on the quality of

life.[9 10] Interestingly, CD can also occur despite the quiescence of other SLE manifestations.[11]

The pathophysiology of NPSLE, including CD, remains poorly understood although there are several proposed theories. Prior research has shown that inflammatory molecules[12] gain access to the CNS via a perturbed blood–brain barrier (BBB)[13], brain–CSF barrier (choroid plexus), meningeal barrier and glymphatic system and result in direct stimulation of neurons and microglia.[11 14] Microglia are antigen-presenting cells in the CNS that are also important for fine-tuning neuronal connections.[3] Microglia are thought to play a role in the loss of neuronal dendrites and are activated by a variety of inflammatory molecules.[5] Injection of SLE serum, and specifically SLE IgG, into mouse CSF has been shown to result in microglial activation and production of proinflammatory cytokines, suggesting that peripheral immune mediators play a role in inducing CNS inflammation via microglia.[15–17] Microglia have been shown to remain activated for many months beyond an initial CNS insult, which is a speculative aetiology for the disconnection between SLE disease activity and CD.[18]

The renin–angiotensin system (RAS) is important in haemodynamic and mineralocorticoid homeostasis and also includes multiple neuroactive peptides that activate microglia and contribute to neuroinflammation in CD.[5] Inactive angiotensin I is converted into active angiotensin II by ACE which is expressed throughout the body including in neurons.[5] Angiotensin II receptor 1 blockers (ARBs) directly block angiotensin II at its site of action, while ACE inhibitors block the conversion of angiotensin I to angiotensin II. Some of these agents, such as captopril, lisinopril, ramipril and perindopril, cross the BBB and are termed 'centrally acting'.[19] ACE inhibitors and ARBs are cornerstones of the management of hypertensive, cardiovascular and proteinuric renal disorders. In patients with SLE, they are indicated for the treatment of hypertension and proteinuria in the case of lupus nephritis.[20]

Angiotensin II has been shown to cause microglial activation and direct neuronal injury/cell death at high levels.[5] RAS suppression has also been shown to result in lower levels of bradykinin which suppresses microglial activation in mice.[5] Furthermore, direct activation of microglia by renin via the prerenin receptor and stimulation of the production of proinflammatory cytokines has been demonstrated in rodent microglia.[21] Pretreatment of microglia with angiotensin II resulted in enhanced proinflammatory cytokine secretion induced by renin.[21] These findings suggest that ACE inhibitors may be a promising emerging therapy for CD partially via inhibitory effects on microglial activation. Supporting this theory, centrally acting ACE inhibitors (cACEi) have been shown to decrease microglial activation and improve cognitive deficits in mice.[19] In a mouse model of *N*-methyl-D-aspartate receptor antibody (DNRAb)[22] -mediated CD, treatment with captopril was shown to lead to less microglial activation compared with mice treated with enalapril, an ACE inhibitor that does not cross the BBB.[5] Furthermore, mice treated with captopril had preserved neuronal dendrite complexity compared with enalapril-treated mice.[5] The degree of complexity was similar to mice lacking DNRAb, and these mice had a normal number of dendritic spines suggesting a reversal of neuronal pathology.[5] Cognitive function, as assessed by the object–place memory task, was preserved in mice treated with captopril and perindopril supporting an ACE-targeted class effect.[5] These findings support the notion that blockade of the RAS, particularly with cACEi, may lead to decreased microglia activation. This may then lead to improved dendritic cell and synapse morphology and a lower incidence of CD.

Investigating cACEi/ARBs as a potential treatment for SLE-associated CD is an important next step in the study of SLE-CD. Clinical trials are now underway although results can be expected to take several years.[5] In the interim, this study aimed to determine whether RAS suppression (use of cACEi and/or ARBs) was associated with lower odds of CD in a 'real-world', prospective cohort of patients with SLE.

METHODS

Design

This is a retrospective study, using data from an ongoing prospective, longitudinal cohort study. Clinical and demographic data were collected from a single academic centre at baseline, 6 and 12 months.

Participants

Patients with consecutive SLE presenting to the University Health Network Lupus Clinic between the dates of July 2016 and November 2021 were considered for this study. Inclusion criteria were: (1) ability to provide informed consent, (2) minimum age of 18 years and (3) English language proficiency (due to the nature of the neurocognitive tests). Exclusion criteria were as follows: (1) physical or mental disability preventing full participation in this study and (2) history of developmental delay or dementia not attributable to SLE.

Procedures

The ACR neuropsychological battery (NB) was administered by a psychometrist to each consenting participant. Details regarding the ACR NB are described elsewhere;[23] the battery measures all major cognitive domains including manual psychomotor function (domain 1), simple attention and processing speed (domain 2), visual-spatial construction (domain 3), language processing (domain 4), learning and memory (domain 5) and executive function (domain 6) (online supplemental table 1). Scores were compared with age-matched and sex-matched controls to obtain z-scores. One minor change was made to the ACR testing protocol: the California Verbal Learning Test[24] was replaced with the Hopkins Verbal Learning Test Revised (HVLT-R).[25] The HVLT-R is a shorter test with more alternative forms for longitudinal testing and was more appropriate for this study.[26] On the

Table 1 Baseline characteristics recorded by CD status

		Primary CD outcome definition			CD definition 2		
		No CD	CD		No CD	CD	
Variable	Value	n=184	n=116	P value	n=205	n=95	P value
Sociodemographics							
Age at enrolment	Mean±SD	41.1±12.1	41.0±12.1	0.95	41.6±11.8	40.0±12.7	0.30
Sex	Female	167 (90.8%)	100 (86.2%)	0.22	188 (91.7%)	79 (83.2%)	0.03†
	Male	17 (9.2%)	16 (13.8%)		17 (8.3%)	16 (16.8%)	
Ethnicity	Black	23 (12.5%)	36 (31.0%)	<0.01†	29 (14.1%)	30 (31.6%)	0.01†
	Caucasian	112 (60.9%)	50 (43.1%)		120 (58.5%)	42 (44.2%)	
	Chinese	22 (12.0%)	11 (9.5%)		23 (11.2%)	10 (10.5%)	
	Others	27 (14.7%)	19 (16.4%)		33 (16.1%)	13 (13.7%)	
Employed or student	Yes (%)	128 (69.6)	67 (57.8)	0.04†	134 (65.4)	61 (64.2)	0.85
Married or common law	Yes (%)	80 (43.5)	40 (34.5)	0.12	84 (41.0)	36 (37.9)	0.61
College or university degree	Yes (%)	151 (82.1)	87 (75.0)	0.14	164 (80.0)	74 (77.9)	0.68
Risk factors							
Currently a smoker	Yes (%)	11 (6.0)	7 (6.0)	0.98	10 (4.9)	8 (8.4)	0.23
Hypertension	Yes (%)	78 (42.4)	59 (50.9)	0.15	89 (43.4)	48 (50.5)	0.25
Antiphospholipid antibody positive*	Yes (%)	29 (15.8)	17 (14.7)	0.80	34 (16.6)	12 (12.6)	0.38
Obesity (BMI>30)	Yes (%)	29 (15.8)	27 (23.3)	0.10	36 (17.6)	20 (21.1)	0.47
Measurements—disease activity/damage, fatigue, pain, depression and anxiety							
SLEDAI-2K score	Mean±SD	3.1±3.3	3.6±4.5		3.1±3.5	3.7±4.3	0.16
	Median (IQR)	2.0 (0.0–4.0)	2.0 (0.0–4.0)	0.78	2.0 (0.0–4.0)	2.0 (0.0–6.0)	0.37
SDI score excluding CD	Mean±SD	1.0±1.4	1.1±1.5		1.1±1.5	0.8±1.2	0.15
	Median (IQR)	0.0 (0.0–1.0)	1.0 (0.0–2.0)	0.32	1.0 (0.0–2.0)	0.0 (0.0–1.0)	0.24
Fatigue Severity Scale (FSS score)	Mean±SD	4.5±1.9	4.9±1.7	0.03†	4.6±1.8	4.7±1.7	0.62
SF-36 Vitality score	Mean±SD	46.0±26.2	39.9±24.5	0.06	43.1±26.8	44.9±23.0	0.61
SF-36 Bodily Pain score	Mean±SD	57.9±28.5	49.3±26.8	0.01†	56.1±28.2	51.5±27.8	0.19
Beck Depression Inventory score—II	Mean±SD	16.0±12.8	19.5±13.0	0.02†	16.4±12.7	19.5±13.3	0.05
Beck Anxiety Inventory score	Mean±SD	16.8±12.8	21.0±14.2	<0.01†	16.9±12.6	21.7±14.7	<0.01†
SLE medications							
Corticosteroids use	Yes (%)	91 (49.5)	54 (46.6)	0.62	102 (49.8)	43 (45.3)	0.47
Corticosteroids dose (mg/day)	Mean±SD	4.5±7.7	5.0±9.0	0.59	4.9±8.5	4.3±7.7	0.60
Corticosteroids cumulative dose	Median (IQR)	19845 (5703–49 089)	16751 (4815–45 280)	0.38	20383 (5945–50 403)	11635 (4800–40 721)	0.04†
Antimalarial use	Yes (%)	152 (82.6)	92 (79.3)	0.48	166 (81.0)	78 (82.1)	0.82
Azathioprine use	Yes (%)	34 (18.5)	17 (14.7)	0.39	41 (20.0)	10 (10.5)	0.04†
Cumulative dose of azathioprine (g/kg)	Mean±SD	0.9±2.6	0.4±1.3	0.06	0.9±2.5	0.2±0.8	0.01†
Immunosuppressive treatment excluding azathioprine use	Yes (%)	78 (42.4)	45 (38.8)	0.54	84 (41.0)	39 (41.1)	0.99
Cyclophosphamide use	Yes (%)	2 (1.1)	0 (0.0)	0.26	2 (1.0)	0 (0.0)	0.33
Ciclosporin use	Yes (%)	1 (0.5)	1 (0.9)	0.74	1 (0.5)	1 (1.1)	0.58
Methotrexate use	Yes (%)	15 (8.2)	10 (8.6)	0.89	15 (7.3)	10 (10.5)	0.35

Continued

Table 1 Continued

Variable	Value	Primary CD outcome definition: No CD n=184	Primary CD outcome definition: CD n=116	P value	CD definition 2: No CD n=205	CD definition 2: CD n=95	P value
Mycophenolate use	Yes (%)	60 (32.6)	36 (31.0)	0.78	66 (32.2)	30 (31.6)	0.92
Belimumab use	Yes (%)	9 (4.9)	5 (4.3)	0.82	10 (4.9)	4 (4.2)	0.80
Rituximab use	Yes (%)	1 (0.5)	1 (0.9)	0.74	1 (0.5)	1 (1.1)	0.58
ACEi or ARB treatment							
Use of ACEi/ARB within 6 months	Yes (%)	40 (21.7)	28 (24.1)	0.63	47 (22.9)	21 (22.1)	0.87
Cumulative dose of ACEi/ARB (mg/kg)	Mean±SD	41.2±171.1	44.7±141.4		42.3±159.0	43.1±163.0	
	Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.36	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.66
Use of cACEi/cARB within 6 months	Yes (%)	29 (15.8)	24 (20.7)	0.28	37 (18.0)	16 (16.8)	0.80
Cumulative dose of cACEi/cARB (mg/kg) (assigned 0 to non-centrally acting)	Mean±SD	40.1±170.9	44.4±141.4		41.3±158.9	42.7±163.1	
	Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.32	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.65

*Antiphospholipid antibodies included: anticardiolipins IgG and IgM and lupus anticoagulant. P value from Mann-Whitney *U* test, Fisher's exact test, χ^2 test or *t*-test.
†Statistically significant, p-value ≤0.05.
ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; cACEi, centrally acting ACE inhibitor; cARB, centrally acting angiotensin receptor blocker; CD, cognitive dysfunction; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SF-36, 36-Item Short Form Survey; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2000.

day of cognitive testing, clinical and demographic data were recorded.

Predictors

The primary predictor of this study was the total cumulative lifetime dose of cACEi/cARB (fosinopril, lisinopril, perindopril, ramipril, trandolapril, candesartan and valsartan) up to the date of cognitive testing, recorded as an equivalent ramipril dose. Participants who previously took these medications but stopped >6 months prior to the study were excluded. The following ACEi/ARB are not considered to be centrally acting, and data regarding their use were not included with respect to the primary outcome: enalapril, quinapril, irbesartan, losartan and olmesartan. The chart used for the calculation of equivalent cACEi/cARB dosing is available in online supplemental table 3. The secondary predictor was the use of cACEi/cARB at the time of cognitive testing, recorded as a binary variable.

Outcome measures

The primary outcome of this study was cognitive dysfunction (CD) which was recorded as a binary variable. The primary definition of CD was as follows:

- Impairment in two or more cognitive domains.
  - Domains 1–4 were impaired if one or more tests had a z-score ≤−1.5.
  - Domains 5–6 were impaired if two or more tests had a z-score ≤−1.5.

Table 2 Multivariable model for our primary CD outcome measure and selected variables

Independent variable	Multivariable analysis: OR	Lower 95% CI of OR	Upper 95% CI of OR	P value
Female versus male	0.28	0.07	1.20	0.09
Caucasian versus non-Caucasian	0.19	0.08	0.48	<0.01*
Employed or student versus others	0.33	0.13	0.83	0.02*
College or university degree	0.38	0.13	1.13	0.08
Fatigue Severity Scale (FSS score)	1.33	1.07	1.64	<0.01*
Cumulative dose of azathioprine (g/kg)	0.70	0.53	0.91	<0.01*
Immunosuppressive use excluding AZA	0.43	0.18	1.02	0.06

Selected out of the model: use of cACEi/cARB and cumulative dose of cACEi/cARB.
*Statistically significant, p-value ≤0.05.
AZA, azathioprine; cACEi, centrally acting ACE inhibitor; cARB, centrally acting angiotensin receptor blocker; CD, cognitive dysfunction.

Table 3 Multivariable model for our *CD definition 2* CD outcome measure and selected variables

	Multivariable analysis			
Independent variable	OR	Lower 95% CI of OR	Upper 95% CI of OR	P value
Female versus male	0.50	0.22	1.13	0.09
Caucasian versus non-Caucasian	0.61	0.36	1.04	0.07
Hypertension	1.41	0.84	2.36	0.19
Antiphospholipid antibody positive	0.54	0.25	1.15	0.11
Cumulative dose of azathioprine (g/kg)	0.81	0.68	0.96	0.02
Belimumab use	0.39	0.11	1.38	0.15

Selected out of the model: use of cACEi/cARB and cumulative dose of cACEi/cARB.
cACEi, centrally acting ACE inhibitor; cARB, centrally acting angiotensin receptor blocker; CD, cognitive dysfunction.

We performed sensitivity analyses, which examined an additional definition of CD:

- CD definition 2: Impairment in one or more cognitive domains.
  - Domains 1–4 were impaired if one or more tests had a z-score ≤–2.5.
  - Domains 5–6 were impaired if two or more tests had a z-score ≤–2.5.

Statistical analysis

Analyses were completed using SAS statistical software (Cary, North Carolina, USA). We calculated 80% power to detect a statistically significant effect based on a minimum sample size of 92 participants in each group, and assuming event rates of 30% and 50% in treatment and control groups, respectively. P-values were considered statistically significant at ≤0.05, and two-sided testing was used. Data were inspected to assess for any data not missing at random and to search for any non-plausible values. Participant visits with all cognitive data missing were removed from the analysis. Also, data determined to not be missing at random were excluded from the analysis. All missing data, other than cognitive test scores, were addressed through multiple imputations except for cognitive test scores. Five imputed datasets using the SAS 'MI' procedure were created. Analyses were performed using each dataset with results pooled together using the SAS 'MIANALYZE' procedure. Descriptive baseline statistics were recorded as mean±SD for normally distributed continuous variables, median with IQR for variables that were not normally distributed and as a number and per cent for ordinal variables. Participant characteristics based on cACEi/cARB use were also recorded. Mann-Whitney *U* test, Fisher's exact test, χ^2 test or *t*-test were used, where appropriate, to determine any statistically significant differences in baseline characteristics.

Generalised linear mixed (GLM) models were created with respect to each predictor and outcome and were performed using the SAS 'GLIMMIX' procedure to account for both interindividual and intraindividual effects. A regression model was created based on clinical relevance and included the following covariates: Systemic Lupus International collaborating Clinics/American College of Rheumatology Damage Index (SDI)[27] score (modified to exclude CD), Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K)[28] score, presence of additional CD risk factors not captured elsewhere (hypertension, obesity and/or active smoker), antiphospholipid antibody positivity (lupus anticoagulant, anti-cardiolipin), azathioprine use (azathioprine use and dose were singled out from other immunomodulators due to its significance in previous research,[29] use of other immunomodulators (antimalarials, belimumab, calcineurin inhibitor, cyclophosphamide, methotrexate, mycophenolate, rituximab), Beck Depression Inventory score-II (BDI-II),[30] Beck Anxiety Inventory score (BAI),[31] age in years, sex (male vs female), ethnicity (black, Caucasian, Chinese vs other), employment status (employed or full-time student vs other), marital status (married or common-law partner vs other) and education level (completion of a College or University degree vs not).

Table 4 Baseline distribution of propensity scores by treatment status prior to stratification

Use of cACEi or cARB within 6 months	No of observations	Minimum	Lower quartile	Median	Upper quartile	Maximum
No	247	0.01	0.06	0.11	0.18	0.67
Yes	53	0.04	0.14	0.28	0.43	0.78
Overall	300	0.01	0.07	0.13	0.23	0.78

cACEi, centrally acting ACE inhibitor; cARB, centrally acting angiotensin receptor blocker.

Table 5 Baseline propensity scores by quartiles and cACEi/cARB use

Quartile	Propensity score range	Use of cACEi or cARB (no of participants)		
		Yes	No	Total at baseline
1	0.00–0.07	3	72	75
2	0.06–0.13	8	67	75
3	0.17–0.23	11	64	75
4	0.23–0.78	31	44	75
	Total	53	247	300

cACEi, centrally acting ACE inhibitor; cARB, centrally acting angiotensin receptor blocker.

Additional sensitivity analyses were performed using propensity score (PS) stratification and matching.[32] PS methods aim to balance patient characteristics and likelihood of cACEi/cARB treatment in each stratum, seeking to mimic randomisation.[33] Propensity scores were generated for each participant using logistic regression and including each aforementioned covariate. The dependent variable for PS generation was cACEi/cARB use. Participants were stratified based on PS percentile (1st–24th percentile, 25th–49th percentile, 50th–74th percentile and 75th–100th percentile), and a GLM model regression was then repeated within each PS strata. Then, participants treated with cACEi/cARB were matched to multiple (if available or 1:1 if not) participants not treated with cACEi/cARB based on a calliper less than 0.2 of the logit of individual PS.[32] Conditional logistic regression models were performed at three time points between matched patients to estimate the odds of CD with respect to treatment status.

In our two final sensitivity analyses, we first examined the relationship of cACEi/cARB use with the most commonly affected cognitive domain in our cohort (domain 5—learning and memory, demonstrated in previous studies[34]) by comparing mean z-scores between treated and untreated groups using Student's *t*-test. Given our small number of participants using cACEi/cARB, we reasoned that using the z-score as a continuous variable would increase statistical power and that examining a single domain may reduce statistical 'noise' in the results. Second, to control for any possible effects of combining multiple cACEi/cARBs as one variable, we examined the association of the most commonly used cACEi/cARB in our cohort (ramipril) with respect to CD status.

RESULTS

Three hundred one participants were recruited for the study. One participant was removed from the analysis as they were missing all cognitive test results. The results shown below are from 300 participants and represent 676 visits.

Missing data

Data from the motor function domain were missing in a large proportion of participants and determined to be missing not at random but because participants with active arthritis were not able to fully engage in this subset of testing due to pain. Therefore, the motor domain test

Table 6 Multivariable model* for cognitive dysfunction (CD) versus cACEi/cARB use,† stratified by propensity score quartiles

Propensity score groups by quartiles	Primary CD definition‡		CD definition 2§	
	OR (95% CI)	P value	OR (95% CI)	P value
1—PS between 0 and 0.07 (n=163 visits)	N/A¶	N/A¶	2.00 (0.05, 82.65)	0.71
2—PS between 0.07 and 0.13 (n=159 visits)	1.66 (0.21, 13.15)	0.63	1.09 (0.21, 5.62)	0.92
3—PS between 0.13 and 0.23 (n=175 visits)	0.39 (0.04, 3.82)	0.42	1.53 (0.33, 7.04)	0.58
4—PS between 0.23 and 1 (n=179 visits)	0.54 (0.08, 3.63)	0.53	0.86 (0.36, 2.04)	0.73

*Propensity scores included as covariates.
†Predictor after adjusting PS in the model: cACEi or cARB within 6 months.
‡Z-sores of −1.5 in two cognitive domains.
§Z-sores of −2.5 in one cognitive domain.
¶0 participants in this subcohort.
cACEi, centrally acting ACE inhibitor; cARB, centrally acting angiotensin receptor blocker; N/A, not available; PS, propensity score.

Table 7 Propensity score–matched multivariable conditional logistic regression models for cognitive dysfunction (CD) versus cACEi/cARB use

Time point	Primary CD definition* OR (95% CI)	P value	CD definition 2† OR (95% CI)	P value
Baseline (n=52 cases+98 controls)	1.15 (0.58, 2.27)	0.69	0.96 (0.47, 1.95)	0.90
Six months (n=37 cases+59 controls)	1.00 (0.40, 2.49)	1.00	0.85 (0.28, 2.58)	0.78
One year (n=36 cases+60 controls)	0.65 (0.18, 2.38)	0.52	0.38 (0.10, 1.44)	0.15

Cases: those taking cACEi/cARB. Controls: those not taking cACEi/cARB.
*Z-sores of −1.5 in two or more cognitive domains.
†Z-sores of −2.5 in one or more cognitive domain.
cACEi, centrally acting ACE inhibitor; cARB, centrally acting angiotensin receptor blocker.

scores were excluded from the analysis. Data were also missing (per cent in brackets) from body mass index (2.5%), fatigue score (19.8%), BDI-II (17.9%) and BAI (19.8%) but were deemed at random and so were imputed before being used in the regression models.

Baseline characteristics

The majority of participants were females (n=267, 89%), Caucasian (n=162, 54%) and college or university educated (n=238, 79%). There was a mean age at enrolment of 41±12 years, median SLEDAI score of 2 (0, 4) and median SDI score (excluding CD) of 0 (0, 2). Fifty-three (18%) of participants were taking a cACEi/cARB. Of those taking a cACEi/cARB, the mean cumulative dose was 236±317 mg/kg. A breakdown of specific cACEi/cARBs used is available in online supplemental table 2. Equivalent cACEi/cARB dose calculations are available in online supplemental table 3. Using the primary CD outcome definition, 116 participants (39%) were defined as having CD. For the secondary outcome (CD definition 2), 95 (32%) were defined as having CD. Baseline characteristics listed by CD status are available in table 1.

Our primary CD outcome measures found those with CD were more likely to be Black (p<0.001), have no college or university education (p=0.037), have greater levels of fatigue (p=0.031), pain (p=0.01), depression (p=0.021) and anxiety (p=0.008) (table 1). Using the *CD definition 2*, Black ethnicity and higher anxiety scores were also associated with CD, in addition to the male sex, cumulative steroid dose, azathioprine use and cumulative azathioprine dose (see table 1). No baseline differences were noted for cACEi/cARB use or cACEi/cARB cumulative dose.

Generalised linear mixed models

Multivariable analysis using the primary outcome found ethnicity, employment status, fatigue and cumulative dose of azathioprine to be significantly associated with CD (table 2). Caucasian ethnicity, employment or student status and higher cumulative azathioprine dose each had a protective effect on CD. The use of cACEi/cARB and cACEi/cARB cumulative dose was not associated with CD. Using the *CD definition 2*, our model found only cumulative dose of azathioprine to have a protective effect on CD (table 3).

Propensity score models

Table 4 shows the distribution of propensity scores prior to stratification. Post-stratification, there were 75 patients in each quartile. Baseline propensity of being treated was relatively balanced, although the number of patients treated with cACEi/cARB in the lowest PS strata was small (treatment group, n=3 and control group 2, n=8; table 5). When including the longitudinal data these figures increased but, in some cases, there were zero counts in treated and non-treated groups.

We repeated GLM models in four subcohorts based on their strata obtained through the above steps. Multivariable analysis using cACEi/cARB as the predictor, the primary and secondary definitions of CD as the outcome and PS as the covariate did not yield significant results (table 6).

We matched propensity scores of those taking cACEi/cARB with those not taking for 52 out of 53 patients. Where possible, multiple patients not taking cACEi/cARB were matched with those who were. Using this matched data, our conditional logistic regression for our three study time points (baseline, 6 and 12 months) revealed no differences when using cACEi/cARB as the predictor and the primary definition of CD as the outcome (table 7).

Our two final sensitivity analyses found no significant differences for the cognitive domain 5 tests (online supplemental table 4) or alternative definition of cACEi/cARB (ramipril only) (online supplemental table 5) when examining cACEi/cARB associations with CD in SLE.

DISCUSSION

Our descriptive analysis demonstrates the relatively high prevalence of CD in patients with SLE as reported in the literature. Despite the literature supporting a mechanistic role of a dysregulated renin/aldosterone axis in

SLE-CD,[5 11 19] we did not find that the use of cACEi/cARB was associated with the lower prevalence of CD. There are many possible causes for this discrepancy which coincide with the limitations of our study. These include insufficient power with our small sample size, the heterogeneous disease process of SLE-CD, inherent bias embedded in the retrospective study design and variable cACEi/cARB treatment regimens in our cohort.

In the current study, patients with and without CD were similar in terms of baseline clinical characteristics, disease activity (SLEDAI-2K) and damage (SDI) scores. However, given that this is an observational study, many unaccounted confounders exist and it is not possible to assume that the treated and untreated groups are balanced as they would be in a randomised controlled trial. For example, we did not directly account for factors such as SLE disease heterogeneity. Given the small sample size, we could not analyse subgroups based on specific disease phenotypes or organ systems involved. We also did not account for additional CD risk factors[35–44] including diabetes, social engagement and preclinical cerebrovascular disease. Further, there exists indication bias given the retrospective design: patients with SLE are most frequently prescribed cACEi/cARB for hypertension and renal impairment, each of which may contribute to the development of CD.[45 46] Indication bias can have a profound effect on results, as patients in the treatment groups may have lower baseline cognitive function compared with the non-treatment group. In particular, the high prevalence of hypertension (approximately 50%) raises the possibility of vascular dysfunction as an irreversible contributor to CD in these patients, as evidenced by the well-established link between hypertensive disorders and cerebrovascular disease.[44 45] It is also worth noting that medication non-adherence is a common complication in SLE[47] and was not something we were able to control for within this study when defining those taking the medications of interest in our analyses.

Genetic predisposition may play a role in response to treatment of CD, including response to cACEi/cARBs.[5 48–52] Recent studies have highlighted genetic polymorphisms which may variably modify an individual response to cACEi/cARB with respect to cognition.[53] This further emphasises the heterogeneity of CD and its potential treatments, each of which may have contributed to our results which are discrepant from existing literature examining the association of ACEi use with cognitive function. Additionally, animal models of SLE are genetically homogeneous,[54] whereas human patients with SLE differ greatly in terms of genetic makeup[55] and this may be another possible reason that our findings differ from mechanistic animal studies. Future studies limiting patient heterogeneity may be more likely to identify an effect of cACEi/cARB. As well, the pathophysiology of SLE-CD remains incompletely understood and is believed to be a result of multiple complex ischaemic and inflammatory processes.[3 56] There may be a continuum of various processes ultimately culminating in CD with variable sensitivity to cACEi/cARB depending on the predominant mechanism of CD in specific patients. Improved understanding of CD pathophysiology would allow for a more targeted study of therapy. As well, while cACEi and cARBs have similar effects on RAS suppression, there may be differences in effect between the two classes of medications which we did not account for. Grouping of these two classes of medications was done given the similar end effect of RAS suppression and also given the limited sample size of our cohort. Finally, the dosing regimen of cACEi/cARB currently reflects regimens established for well-studied cardiovascular and renal indications which may be suboptimal to elicit an effect on CD in SLE.

In support of our previous study,[29] we again found azathioprine use to be associated with CD in SLE. This is not surprising as the same cohort was used in both analyses. The association between azathioprine and CD in SLE may be due to its ability to inhibit activation of microglia, as microglia activation has been associated with the development of CD in SLE.[5] This is discussed in more detail in our previous paper.[29]

In summary, the contrast between our study findings and the existing literature from animal models reinforces the notion that CD in SLE is a multifactorial and complex process.[5 11 19 21 57–59] Despite our negative findings, the mounting body of mechanistic evidence supporting the role of cACEi/cARB in patients with CD suggests that further human studies are warranted to investigate cACEi/cARB as a potential treatment for SLE-CD, and in particular randomised controlled trials. This is the first human study, to our knowledge, to examine the association between cACEi/cARB use and SLE-CD. There is currently a randomised clinical trial underway to investigate the potential role of cACE/cARB in SLE-CD and will offer essential insight into this important area of clinical investigation.

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