Influence of Ethnicity on Efficacy of Current Immunosuppressive Protocols in Proliferative Lupus Nephritis

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Background

Recently, variable responses to proliferative LN induction treatments have been observed in different ethnic groups with Hispanics and Blacks tending to respond better to Mycophenolate Mofetil (MMF) than intravenous Cyclophosphamide (IV CYC).[1] Limited data is available for South Asians[2]. Our aim was to examine retrospectively the influence of ethnicity on LN outcome in our large single centre cohort of patients.

Methods

86 SLE patients diagnosed with biopsy proven LN class III/IV between 1992 and 2013 and with a follow-up of at least 6 months were included in this retrospective study. Patients were divided into 3 ethnic groups: South Asians (Bangladesh, India, Pakistan and Sri Lanka), Blacks (African Blacks and Afro-Caribbeans) and White Caucasians. Complete remission (CR) was defined as proteinuria <0.5 g/day and stable or improved serum creatinine. End stage renal disease (ESRD) was defined as GFR <15.

Induction regimens

CYC was given either orally (100-150 mg/day for 3-6 months), or IV as per NIH regimen (6 pulses of monthly IV CYC 0.75 g/m2 of body surface) or Eurolupus regimen (6 infusions of 500 mg fortnightly). MMF was given orally in divided doses with a target dose of 3g/day. Prednisolone was given to all patients 1 mg/kg/day for 4-6 weeks and tapered by 6-9 months.

Results

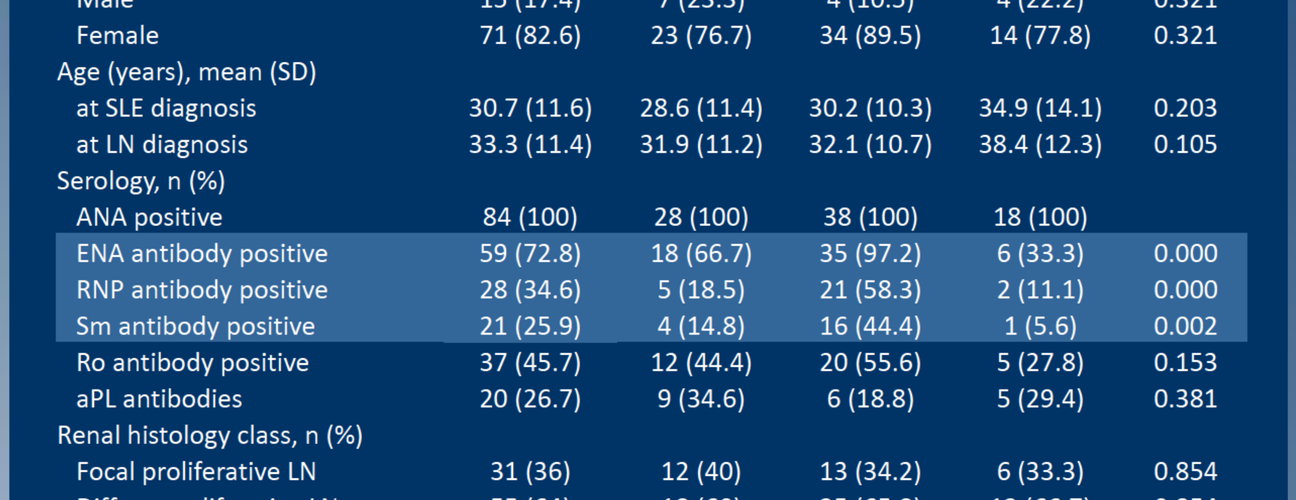
are shown in tables and figures. At time of presentation 9 patients (11.3%) required renal replacement therapy, of which 3 became dialysis independent later. 6 patients with irreversible renal loss on presentation were excluded from analysis. CYC was the induction regimen in 58.8% of LN patients (n=47) with a median cumulative dose of 5.6 g (IQR, 3-9 g) calculated for the first 6 months, whilst 33.8% received MMF (n=27) with median dose of 2 g/day (IQR, 2-2 g). Black patients presenting with worse renal function were more likely to receive CYC than MMF (median creatinine 133 µmol/L vs. 90 µmol/L, respectively, p=027). No difference in baseline biochemical parameters was observed between treatment arms in the other two ethnic groups including the level of proteinuria, serum albumin or creatinine concentrations.

Results 1. Baseline characteristics of LN patients with relapse

	Total (n=86)	South Asian (n=30)	African/Afro-Caribbean black (n=38)	White Caucasian (n=18)	p-value
Gender					
Male	15 (17.4)	7 (23.3)	4 (10.5)	4 (22.2)	0.321
Female	71 (82.6)	23 (76.7)	34 (89.5)	14 (77.8)	0.321
Age (years), mean (SD)					
at SLE diagnosis	30.7 (11.6)	28.6 (11.4)	30.2 (10.3)	34.9 (14.1)	0.203
at LN diagnosis	33.3 (11.4)	31.9 (11.2)	32.1 (10.7)	38.4 (12.3)	0.105
Serology, n (%)					
ANA positive	84 (100)	28 (100)	38 (100)	18 (100)	
ENA antibody positive	59 (72.8)	18 (66.7)	35 (97.2)	6 (33.3)	0.000
RNP antibody positive	28 (34.6)	5 (18.5)	21 (58.3)	2 (11.1)	0.000
Sm antibody positive	21 (25.9)	4 (14.8)	16 (44.4)	1 (5.6)	0.002
Ro antibody positive	37 (45.7)	12 (44.4)	20 (55.6)	5 (27.8)	0.153
aPL antibodies	20 (26.7)	9 (34.6)	6 (18.8)	5 (29.4)	0.381
Renal histology class, n (%)					
Focal proliferative LN	31 (36)	12 (40)	13 (34.2)	6 (33.3)	0.854
Diffuse proliferative LN	55 (64)	18 (60)	25 (65.8)	12 (66.7)	0.854
Additional membranous LN	18 (20.9)	9 (30)	7 (18.4)	2 (11.1)	0.261
Biochemical variables, median [IQR]					
Proteinuria (g/day)	3.9 [1.8-7.7]	6.3 [1.6-8.8]	3.2 [2.1-6.4]	3.7 [1.7-6]	0.513
Serum albumin (g/L)	29 (21-35)	28 [24-36]	29 [21-33]	31 [20-36]	0.842
Serum creatinine (µmol/L)	110 [80-210]	103 [71-200]	131 [92-269]	100 [67-152]	0.036
Lupus activity markers, n (%)					
Raised anti-dsDNA	63 (77.8)	21 (72.4)	31 (88.6)	11 (64.7)	0.104
Low complement C3	56 (72.7)	18 (69.2)	26 (76.5)	12 (70.6)	0.803
Low complement C4	56 (72.7)	17 (65.4)	27 (79.4)	12 (70.6)	0.470

n indicates number of patients; SLE, systemic lupus erythematosus; LN, lupus nephritis; ANA, anti-nuclear antibody; ENA, extractable nuclear antigens; dsDNA, double-stranded DNA; aPL, anti-phospholipid

Results 2. Complete remission rates at 6 (left) and 24 months (right)

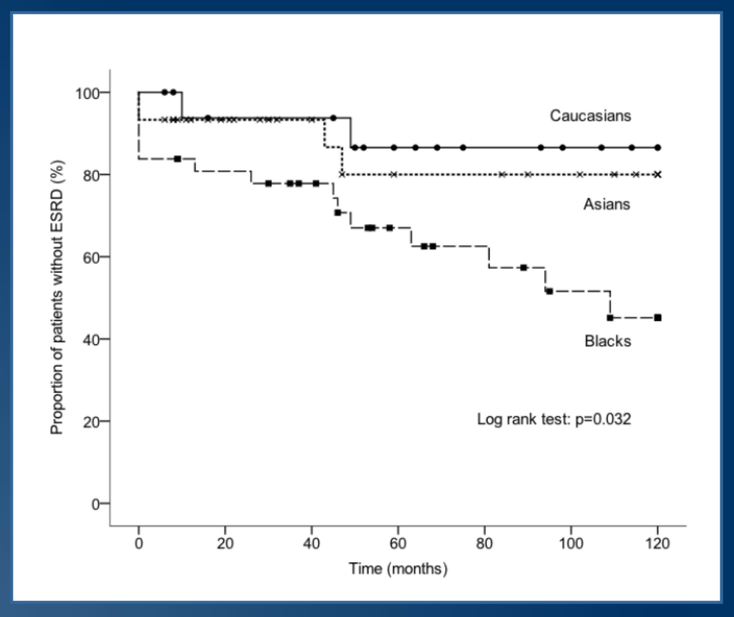


Results 3. Factors predicting LN remission by 24 months

Prognostic factors	Univariate analysis OR (95% CI)	p-value	Multivariate analysis OR (95% CI)	p-value
Baseline demographics				
Male gender	0.66 (0.17-2.62)	0.553	0.00 (0.00-77.64)	0.200
Age at LN diagnosis[1]	1.00 (0.95-1.04)	0.841	1.06 (0.93-1.20)	0.420
Ethnicity				
Caucasian	1 (ref)		1 (ref)	
Asian	0.40 (0.07-2.22)	0.292	0.47 (0.01-32.36)	0.724
Black	0.19 (0.04-0.99)	0.049	1.30 (0.04-38.19)	0.878
Baseline clinical and serological variables				
Diffuse LN (class 4)	0.165 (0.04-0.63)	0.009	0.06 (0.00-4.71)	0.206
Serum creatinine (µmol/L)[2]	0.99 (0.99-1.00)	0.017	0.98 (0.95-1.00)	0.049
Proteinuria (g/24 hours)	0.93 (0.81-1.07)	0.306	0.77 (0.42-1.43)	0.413
Raised dsDNA	0.46 (0.13-1.56)	0.212	0.66 (0.01-33.46)	0.837
Low C3	0.39 (0.12-1.31)	0.128	0.12 (0.27-77730)	0.120
Low C4	0.27 (0.08-0.90)	0.030	0.06 (0.00-4.71)	0.312
Induction treatment				
Induction regimen				
Cyclophosphamide	1 (ref)		1 (ref)	
Mycophenolate mofetil	2.52 (0.80-7.98)	0.116	1089 (0.02-60745834)	0.210
Concomittant treatment				
Hydroxychloroquine	2.07 (0.58-7.40)	0.261	78.47 (0.24-26022.16)	0.141
ACEi/ARB	2.72 (0.83-8.97)	0.099	22.26 (0.40-1243.65)	0.131
Statin	0.32 (0.09-1.20)	0.091	11.76 (0.02-7397.03)	0.638

[1]OR per increase of 1 year; [2]OR per increase of 1 µmol/L; LN indicates lupus nephritis; dsDNA, double stranded DNA; C3, complement 3; C4, complement 4; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; OR, odds ratio; CI, confidence interval

Results 4. Kaplan Meier estimate of 10-year renal survival



Results 5. Cox proportional hazards model for predictors of ESRD by 10 years

Predictor variable	Univariate analysis HR (95% CI)	p-value	Multivariate analysis HR (95% CI)	p-value
Baseline demographics				
Male gender	0.89 (0.20-4.02)	0.879	6.37 (0.56-72.53)	0.136
Age at LN diagnosis[1]	1.03 (0.98-1.08)	0.224	1.02 (0.96-1.08)	0.579
Ethnicity				
Caucasian	1.00 (ref)		1.00 (ref)	
Asian	0.61 (0.08-4.35)	0.618	0.07 (0.00-2.45)	0.141
Black	2.09 (0.45-9.73)	0.350	1.52 (0.20-11.56)	0.684
Baseline biochemical variables				
Proteinuria (g/day)[2]	0.99 (0.84-1.17)	0.943	1.02 (0.78-1.34)	0.882
eGFR (ml/min/1.73m^2)				
>60	1.00 (ref)		1.00 (ref)	
30-60	4.92 (0.51-47.37)	0.168	2.24 (0.18-28.36)	0.533
<30	25.51 (3.23-201.75)	0.002	32.55 (3.70-286.64)	0.002

[1]HR per increase of 1 year; [2]HR per increase of 1 g/24 hours; ESRD indicates end stage renal disease (GFR < 15 ml/min); eGFR, estimated glomerular filtration rate; LN, lupus nephritis; HR, hazard ratio; CI, confidence interval

Conclusion

This study provides new data on South Asian patients from the Indian Subcontinent with LN; and although there was no statistically significant difference between treatment groups there was a greater tendency to respond better to MMF than CYC. In addition, MMF tended to achieve higher remission rates in Blacks, although we noted that severe disease was more likely to be treated with CYC in this ethnic group. In line with previous studies, long term renal survival rate was significantly lower in Blacks compared to Asians or Caucasians, and low GFR on presentation was an independent risk factor for poor 10-year renal survival.

References

[1] Isenberg D et al. Influence of race/ethnicity on lupus nephritis treatment: the ALMS study. Rheumatology 2010; [2] Das U et al. Pulse Cyclophosphamide in severe lupus nephritis: Southern Indian Experience. Saudi J Kidney Dis Transpl 2010.

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H) Clinical Nephrology, primary and secondary glomerulonephritis.

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