Lupus Nephritis: A Different Disease in European Patients?

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Key Words
Lupus nephritis · Ethnicity · Prevalence · Outcome · Cyclophosphamide · Mycophenolate mofetil

Abstract
Background: Lupus nephritis (LN) is still associated with significant mortality and substantial risk of progression to end-stage renal failure. Its outcome is related to the class and severity of LN and response to treatment, and it is poorer in patients with renal relapses. Ethnicity has a relatively well-defined impact on the outcome of the patients and their response to treatment and must always be taken into consideration in treatment decisions. Summary: In this article, we provide a review of the impact of ethnicity on the prevalence of systemic lupus erythematosus (SLE), the proportion of patients with SLE developing LN, outcomes of SLE and LN and response of LN to treatment. In European patients, the prevalence of SLE and the proportion of SLE patients with LN are lower and the outcome of LN is better than in nonwhite populations. European patients may respond better to some modes of treatment [e.g. cyclophosphamide (CYC) or rituximab] and may be less frequently refractory to treatment compared to black patients with LN. Although these differences may be largely genetically driven, socioeconomic factors (poverty, education, insurance, access to health care and adherence to treatment) may also play a significant role in some disadvantaged patients. Key Message: Treatment of LN may be different in patients with different ethnicity. Less aggressive disease in European patients may better respond to less aggressive treatment. Treatment of LN in nonwhite patients may require newer (more effective) therapeutic approaches, but targeting negative socioeconomic factors might be even more effective.

Facts from East and West:
(1) The prevalence of SLE is lower among Caucasians than other ethnicities. A higher prevalence is observed among Asians and African Americans, while the highest prevalence is found in Caribbean people. The prevalence of LN in Asian SLE patients is much higher than in Caucasians as well. However, the 10-year renal outcome and renal survival rate appear to be better in Asians. (2) Polymorphisms of genes involved in the immune response, such as Fcγ receptor, integrin alpha M, TNF superfamily 4, myotubularin-related protein 3 and many others, might be partly responsible for the differences in prevalence between the different ethnic groups. European ancestry was shown to be associated with a decrease in the risk of LN even after adjustment for genes most associated with renal disease. (3) Access to health care is a key determinant of disease progression, treatment outcome and the management of complications such as infections, particularly in South Asia, and might also explain disparities between clinical outcomes. (4) The efficacy of low-dose CYC for lupus nephritis in Asia, see Yap and Chan Kidney Dis 2015;1:100–109.
combined with corticosteroids for induction treatment of LN was proved in European Caucasian patients. This treatment is also used in Asia, although no formal evaluation of efficacy and safety in comparison with other treatment regimens exists in this population. The efficacy of mycophenolate mofetil (MMF) is similar to that of CYC, and similar between Asians and Caucasians. MMF may be more effective than CYC in inducing response in high-risk populations such as African American or Hispanic patients. MMF might cause less infection-related events in Asians, but its high cost prevents broader usage at present. (5) For maintenance therapy, corticosteroid combined with azathioprine (AZA) or MMF is used worldwide, with a broadly similar efficacy of both treatments, although there are data suggesting that in high-risk populations (e.g. African Americans) MMF may be more effective in preventing renal flares. AZA is often preferred in Asia due to economic constraints and because of its safety in pregnancy. (6) Alternative therapies under investigation include rituximab, which might be more efficient in Caucasians, as well as belimumab. Recent Japanese and Chinese studies have indicated a potential benefit of tacrolimus as a substitute for or in addition to CYC or MMF (dual or triple immunosuppression). Mizoribine is used in Japan exclusively.

Ethnicity and Prevalence of Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is more frequent in nonwhite populations [1]. The prevalence of SLE is higher in African Americans and Hispanics compared to whites and Asians [2]. Absolute data on the prevalence and incidence of SLE in different ethnicities, however, vary widely (table 1). In different studies in the USA [3, 4], the prevalence of SLE was higher among women in African Americans, whites, and Hispanics than in Asians/Pacific Islanders [4].

In the UK, the prevalence of SLE was, however, consistently higher in Asians compared to whites [5, 6], especially when Chinese Asians (in some studies with a prevalence almost twice as high) were clearly separated from Indian Asians [7, 8]. A recent UK retrospective cohort study also confirmed the highest incidence and prevalence of SLE in people with black Caribbean ethnicity and a higher prevalence in Asian compared to white patients [9]. Similarly, in a large French nationwide study, the prevalence of SLE was also much higher in the Caribbean overseas areas and lowest in the French northwestern metropolitan territories [10].

Ethnicity and Prevalence of Lupus Nephritis

Renal disease in SLE is, undoubtedly, less frequent in patients with SLE of European origin both in Latin America and the USA (43.7 and 22.7% of SLE patients affected, respectively) compared to patients of Hispanic (Mestizo; 58.3 and 59% of SLE patients affected, respectively) and of African ancestry (55.3 or 54.4% of SLE patients affected, respectively) [11, 12]. In the UK, lupus nephritis (LN) is twice as frequent in blacks with SLE compared to whites (62 vs. 32%) [13].

Renal disease is also much more frequent in Asians with SLE compared to white Europeans. The cumulative incidence of LN in Chinese patients with SLE was reported to be as high as 75.8% [14] and 56.6% [15], while in Malayans it was 66.7% and in Indians 69.7% [13] and 57% [16] compared to only 27.7% in whites [17]. During a 10-year follow-up, LN occurred in only 27% of 1,000 white European patients with SLE [18] compared to 57% of 442 Chinese patients from Hong Kong during a follow-up of 8.5 years [15].

The prevalence of biopsy-proven LN in the UK was much higher in Chinese women compared to Indo-Asian and white women (110.3 vs. 21.4 and 5.6 per 100,000 patients, respectively) and in Chinese men compared to Indo-Asian and white men (20.3 vs. 4.1 and 1.1 per 100,000 patients, respectively), but the prevalence of biopsy-proven LN was similarly high in Chinese and Afro-Caribbean patients [19]. Compared to whites, the age-standardized prevalence of biopsy-proven LN was 3.8 times higher in Indo-Asian, 18.6 times higher in Afro-Caribbean and 19.2 times higher in Chinese citizens of the UK [19]. In Europeans and Asians, the prevalence of LN was highest at the age of 35–74 years [8, 19], whereas it peaked earlier, at the age of 15–44 years, in black Americans.

Genetic Susceptibility to SLE and LN

The striking difference in the prevalence of LN has always been suspected to be strongly genetically driven. Since the 1970s, but mainly in the last decade, an ever increasing number of genes (more than 90 on almost any chromosome [20]) predisposing to SLE have been identified [21], including multiple alleles in the HLA system, complement components C1q, C4 and C2 and other genes participating in immune regulation, interferon and cytokine pathways, e.g. PTPN22, IRF5 and TNFSF4. A meta-analysis of three genome-wide association studies in women with SLE identified several further non-major
histocompatibility complex (MHC) genes associated with the susceptibility to LN (PDGFRA, GSX2, SLC5A11, ID4, HAS2 and SNTB1) [22].

Recent positive natural selection at several loci associated with SLE, e.g. PTPN22, TNFSF4 or ITGAM, was demonstrated [20]. Some of these genes, e.g. TNFSF4, seem to be related to SLE susceptibility and autoantibody production in all studied populations with different ethnicities [23], whereas some of the genes under recent positive selection pressure (e.g. BLK, ITGAM, CLEC16A [20] and PTPN22 [24]) differ between populations with different ethnicity. Several MYH9 polymorphisms seem to be associated with LN only in European patients [25]. The identification of ethnicity-specific genetic factors should help in the better understanding of the pathogenesis of SLE in different ethnic subgroups [26].

Neanderthal admixture of about 1–3% of the gene pool of the genome of the modern people has been recently demonstrated, and it has been suggested that polymorphisms of some genes conferring LN susceptibility (IRF5; G allele enriched in the European population) could have been of Neanderthal origin [27, 28].

Using both gene polymorphisms informative of ancestry and gene polymorphisms in candidate genes for renal disease in SLE in a large study with 1,906 participants, each 10% increase in European ancestry was associated with a 15% decrease in the risk of renal disease even after adjustment for genes most strongly associated with renal disease, i.e. IRF5, BLK, STAT4 and HLA-DRB1 polymorphisms, and socioeconomic factors [28], demonstrating that European ancestry is protective against the development of renal disease in SLE, independently of other known genetic and socioeconomic factors.

On the other hand, it remains to be stressed that ethnicity accounts for less than 8% of the total variance in the risk for renal involvement [29]. Out of this ethnicity-re-

Table 1. Age-adjusted prevalence of SLE and ethnicity

<table>
<thead>
<tr>
<th>Country, area</th>
<th>Study period</th>
<th>Ethnicity</th>
<th>Prevalence</th>
<th>First author [ref.]</th>
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Ethnicity and Outcome of SLE and LN

The outcome of SLE and LN is generally worse in nonwhite, often disadvantaged populations [1], not only because of genetic but also because of socioeconomic factors, including poverty, education, disease awareness, access to health care, compliance and attitudes to the available treatment, including treatment adherence.

Renal disease is the most important predictor of a poor outcome in patients with SLE, decreasing the 10-year survival in SLE from 85 to 75% [32]. Native Americans [hazard ratio (HR) = 1.40] and African Americans (HR = 1.20) have a higher mortality compared to white patients with SLE. On the other hand, Hispanic and Asian patients have lower mortality risks (HR = 0.48 and 0.59, respectively) compared to white patients with SLE [33]. The 10-year survival of SLE was reported to be higher in Europe (78–90%) compared to Asia (44–78%) [8]. Despite huge differences in the gross domestic product among countries, the human development index, which also takes into account access to health care, educational level, availability of physicians and patients’ compliance, seems to be much better related to the outcome of patients with SLE compared to the gross domestic product [34].

Whereas genetic factors are believed to play a role mainly in disease susceptibility, socioeconomic factors associated with ethnicity become more important during the course of the disease with a significant impact on its outcome [35], but genetic factors may still play an important role in the progression of kidney disease in SLE.

In a mixed Brazilian population, MYH9 gene polymorphisms (but not APOL1) were associated with a risk of progression of CKD [36]. In African American patients with SLE, APOL1 G1 and G2 risk alleles were strongly associated with end-stage renal disease (ESRD) even after adjustment for age, sex and ancestry [37].

The incidence of LN seems to be decreasing at least in some parts of Europe, possibly because of earlier detection of SLE and earlier treatment [38]. The increasing prevalence of SLE in the UK [9], despite an annual decline in its incidence by 1.8%, may supposedly result from a better outcome of patients with SLE, but this remains to be confirmed also for nonwhite ethnicities. The outcome of black patients with LN is significantly worse both in terms of patient survival (the 5-, 10- and 15-year patient survival was 76, 65 and 55% in blacks compared to 87, 76 and 70% in whites [13]) and renal survival (the 5-year survival without doubling of serum creatinine was 63% in blacks and 88% in whites [39]).

In a large European study, SLE was demonstrated to be more active in patients with black African descent compared to Caucasian patients in terms of more frequent flares and more frequent severe flares [40]. In a large single-center US LN cohort [41], the mean Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score predicted mortality and organ damage including renal damage, and a higher SLEDAI score was associated with African American ethnicity. In a single-center Australian study [42], Asian ethnicity was associated with more severe SLE, a higher mean and maximum SLEDAI score, a more frequent persistently active disease and renal disease and also a higher proportion of positivity of different autoantibodies (anti-ds-DNA, anti-Ro, anti-La, anti-RNP and anti-Sm), more frequent hypocomplementemia and immunosuppressant use.

The outcome of European patients with LN significantly improved in the last 50 years, and life expectancy of Italian women with LN has even been reported to approach that of the general population [43]. In a British cohort, 5-year mortality decreased by 60% during the 30 years between 1975 and 2005, but in the last decade of the study, there was still a substantial (about 5%) 5-year mor-
A single-center Australian study compared to whites more frequently positive for anti-Ro, anti-nRNP and aggressive course of LN. In black patients, serologic and histologic findings are more frequently associated with a more aggressive course of LN. Black patients with severe LN are more frequently positive for anti-Ro, anti-nRNP and anti-Sm antibodies compared to whites [47].

In a multiethnic US cohort with proliferative LN [46], renal outcome was worse in Hispanic and black patients compared to white patients and in those living in high poverty compared to a better social status, and in the multivariate analysis, poverty and insurance seemed to be even more important than ethnicity, especially in African Americans. In black patients, serologic and histologic findings are more frequently associated with a more aggressive course of LN. Black patients with severe LN are more frequently positive for anti-Ro, anti-nRNP and anti-Sm antibodies compared to whites [47].

The poor renal outcome of black patients with LN may also be partly caused by more severe renal lesions in blacks (WHO class IV lesions in 51% of biopsied blacks vs. 30% of whites [39], WHO class III lesions with >50% of glomeruli involved in 76% of blacks vs. 44% of whites [47]) even within the same WHO class (e.g. cellular crescents and interstitial fibrosis [48]). These characteristics were associated with a much lower remission rate in blacks compared to whites (29 vs. 52%) and a much lower 10-year survival (59 vs. 81%) and renal survival (38 vs. 68%).

Interestingly, studies looking at the prevalence of renal damage in patients with SLE among Asians residing in western countries demonstrated a higher prevalence of damage compared to white patients, which was not confirmed in studies performed in China or Korea, but the increased renal damage in Asian patients was almost uniformly reported [49]. Asian patients may also have a higher rate of LN-associated antibodies, LN and more active glomerulonephritis compared to white patients [50]. A single-center Australian study [51] demonstrated a disproportionate overrepresentation of patients with Asian ethnicity both among patients with SLE and patients with LN, but the distribution of the histological severity of LN was similar among Asian and Caucasian patients.

The outcome of Asian patients with LN was reported not to be better than that of African Americans, and similarly as in African Americans and Hispanics, the outcome varies with geographical regions depending not only on ethnicity but also on socioeconomic factors, e.g. poverty, educational level, cultural factors and access to health care [50]. However, in other studies, the long-term outcome of Asian patients with LN seemed to be comparable to that of Caucasians [52], with only 4.4% of Chinese patients with diffuse proliferative LN treated with oral cyclophosphamide (CYC) developing a doubling of serum creatinine and none of them developing ESRD during 92 months of follow-up [53]. According to a large US survey of patients with ESRD due to LN [54], black and Hispanic patients were less frequently provided with pre-ESRD care than white patients and were less frequently placed on the waiting list for kidney transplantation within the first year after the start of ESRD, which was related to type of health insurance that was much higher in patients with private insurance compared to standard or no insurance).

The increasing standardized incidence rate for LN ESRD among African Americans from 1995 to 2006 and the failure to improve survival in patients with ESRD due to LN during the first 3 years of ESRD [55] suggest that, in African Americans, the current treatment of LN may not be sufficiently effective and/or that there may still be some barriers in the access to health care and/or poor adherence to treatment in disadvantaged minority populations. African Americans with ESRD due to LN have a 27% higher mortality rate compared to whites (this difference is even more marked among patients under the age of 40 years) [56]. They are also more frequently admitted to the hospital for heart failure or hemorrhagic stroke. However, Asian and Hispanic patients with ESRD due to LN, similarly as Asian and Hispanic patients with SLE, have lower mortality rates than whites.

African American recipients of a kidney transplant with LN had an increased risk of graft loss and death compared to non-African Americans, and the risk of graft loss was (only in African Americans) associated with a lower income [57]. African Americans with LN received more kidneys from deceased donors and donors with more than two HLA mismatches and more frequently developed delayed graft function, rejection and recurrent LN compared to Hispanic and Caucasian US patients [58–60]. After adjustment for all these differences, the increased risk of graft failure among African Americans remained nonsignificant [59, 60].

In conclusion, black patients with SLE have more active serology and more severe renal disease compared to white patients, and when the renal disease progresses, not all of them are provided with adequate pre-ESRD care. The outcome of black patients with ESRD due to LN is also poorer compared to whites, and if transplanted, they have a higher risk of graft loss, probably because they more frequently receive grafts from deceased donors and with more mismatches, disclosing once again the impor-
tance of socioeconomic factors in disadvantaged populations. Asian patients with SLE may have a comparable or even better overall survival than their white counterparts, but their renal outcome may be worse than in white patients.

**Ethnicity and Response to Treatment of LN**

Early randomized controlled trials performed by the NIH in patients with LN demonstrated a better renal outcome [61] and a higher remission rate [62] in patients treated with a combination of corticosteroids and CYC compared to corticosteroid only, but at the expense of a very high rate of infections (severe infections in 26% and herpes zoster in 25% of patients) and ovarian failure (52%).

The Euro-Lupus Nephritis Trial (ELNT) [63] demonstrated a comparable efficacy (both in terms of treatment failure and renal remission) of low-dose (cumulative dose of 3 g) and high-dose (cumulative dose of 8.5 g) CYC in (mostly) white European patients with LN, and the very similar efficacy of both therapeutic regimens in European patients was confirmed also during the longer 10-year follow-up [64]. It was repeatedly stressed that it still remains to be demonstrated that a low-dose CYC regimen can be safely used also in patients with LN of other ethnicities including African Americans, Hispanics and Asian patients [65]. A recent trial of abatacept for LN (ACCESS [66]) demonstrated a surprisingly high response rate to low-dose CYC (which was used as a background treatment) in a mostly black (37%) and Hispanic (41%) population. The rate of complete remission (more than 30% in both arms treated with low-dose CYC) was higher than in recent trials of LN (ALMS [67] and LUNAR [68]). Even after using the same criteria for complete response (proteinuria ≤0.5 g/24 h and no worsening of serum creatinine compared to baseline), low-dose CYC in the ACCESS trial [66] was similarly effective as high-dose CYC in the ALMS trial [67] and low-dose CYC in the ELNT trial [63], with complete response achieved in 22, 24 and 23% in the ALMS, ELNT and ACCESS trials, respectively [69]. Although there were some differences in the severity of LN among these trials (the proportion of patients with proteinuria ≥3 g/24 h was lower in the low-dose CYC ELNT trial (42%) and in the low-dose CYC ACCESS trial (52%) compared to the high-dose CYC ALMS trial (60%)), these data suggest that at least the short-term (6-month) efficacy of low-dose CYC may be similar in African Americans and Hispanics as in Caucasian patients [69], especially when high-dose corticosteroids are given concomitantly.

In thus far the largest randomized controlled trial of 358 patients with LN (ALMS study [67]) in a multiethnic population, mycophenolate mofetil (MMF) was not inferior, but also not superior, to high-dose pulsed CYC as induction treatment of active LN in terms of remission rate. A secondary analysis of the ALMS study [70] demonstrated the impact of significant interactions between treatment and race and treatment and region on the primary endpoint rate. CYC and MMF response rates were similar in Asians (53.2 vs. 64.9%, respectively) and whites (56 vs. 54.2%), but significantly less black (40 vs. 53.9%) and Hispanic patients responded to CYC compared to MMF (38.8 vs. 60.9%). Altogether, non-Hispanic ethnicity was an independent predictor of a higher likelihood (twice as high) of complete remission [71].

On the other hand, the incidence of adverse events was similar across ethnic groups (and all infections were less frequent in Asian patients), but serious adverse events were slightly higher among Asians. Whereas African Americans in the CYC arm had a high rate of premature withdrawal from the study, Asian patients treated with CYC had a lower rate of withdrawal from the study compared to patients treated with MMF (5.1 vs. 22.8%) [70].

Those multiethnic patients recruited to the ALMS study who achieved remission were re-randomized to maintenance treatment either with MMF or azathioprine (AZA) [72]. MMF was superior to AZA in terms of treatment failure, renal flare and time to rescue therapy. In a similar study in European (almost exclusively white) patients, maintenance treatment of LN (MAINTAIN) with AZA was similarly effective as maintenance treatment with MMF in terms of time to renal flare [73]. Repeat renal biopsies (in 30 patients at 2 years ± 6 months) also failed to detect any difference between AZA and MMF in terms of both activity and chronicity of the disease [74]. The recently published 10-year follow-up of the MAINTAIN trial [75] demonstrated a positive predictive value of early decrease in proteinuria on long-term renal outcome of patients with LN, but there was no difference in renal outcome and time to renal flare between AZA- and MMF-treated patients. The different results of the maintenance phase of the ALMS study and the MAINTAIN trial suggest that the better efficacy of the MMF-based maintenance compared to the AZA-based maintenance may be restricted to nonwhite patients only, possibly due to a poorer response to CYC in black compared to white patients [76].

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Refractory LN referred to the off-label treatment with rituximab may also be more frequent in nonwhite patients [77]. Black race, however, may be one of the predictors of poor response to rituximab [78, 79], and a relatively large proportion of black patients (26%) may partly explain the negative results of the only randomized controlled trial with rituximab (LUNAR [68]) compared to the very positive data reported in observational studies mostly in European white patients [80].

African American patients with SLE were demonstrated to be less willing to receive CYC when their LN was worsening, and the difference remained significant even after adjusting for socioeconomic and psychosocial variables. Trust in the physician and the perception of treatment effectiveness were the most important determinants of accepting treatment with CYC in African American patients [81]. Race together with income and a higher perception of CYC effectiveness persisted as an independent predictor or treatment preference (willingness to receive CYC) even after adjustment for socioeconomic factors, clinical context and patients’ perception of physicians [82].

In Europe, Caucasian patients with active LN may still initially be treated with a similar efficacy with either low-dose CYC or MMF, and for the maintenance phase of the treatment, MMF is comparable to AZA. Rituximab seems to be effective in most patients with refractory SLE and LN. The applicability of these recommendations to more severe disease in African American, Hispanic or Asian patients remains uncertain, and long-term observational data and randomized controlled trials in multiethnic populations of patients with LN are clearly warranted.

**Conclusions**

LN is less common in white (Caucasian) SLE patients compared to black, Hispanic or Asian patients and may be less severe with a better outcome in whites compared to other ethnicities, which may be related both to genetic and socioeconomic factors. Response to treatment (CYC and possibly also rituximab) may be worse in African American compared to white patients, and adverse events of treatment may also differ between different ethnicities. Further studies elucidating the impact of ethnicities on the risk, severity, response to treatment and outcome are warranted including both observational data from large multiethnic cohorts and randomized controlled trials.

**Disclosure Statement**

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