Race and the response to therapies for lupus: how strong is the evidence?

Systemic lupus erythematosus is a heterogeneous autoimmune disease caused by genetic and environmental factors. It is recognized that patients from different racial backgrounds have considerable variability in the presentation and course of their disease. There is also emerging evidence that response to treatment may vary between different racial groups and geographical locations. This includes the finding that mycophenolate mofetil appears to be the therapy of choice for lupus nephritis in individuals of African and Hispanic origin. The new ACR guidelines for the treatment of lupus nephritis reflect this evidence by using racial groups to help define the choice of treatment. The strength of evidence for variation in treatment response between racial groups in systemic lupus erythematosus and how this might alter prescribing is presented in this review.

KEYWORDS: race ■ systemic lupus erythematosus ■ treatment

Anna Ewa Litwic[1],
Melonie Kannamma
Sriranganathan[1]
& Christopher John
Edwards*[1,2]

[1]Rheumatology Department,
University Hospital Southampton NHS
Foundation Trust, Tremona Road,
Southampton, SO16 6YD, UK
[2]National Institute for Health Research
Wellcome Trust Clinical Research
Facility, University Hospital
Southampton NHS Foundation Trust,
Southampton, UK
*Author for correspondence:
Tel.: +44 2380 798723
Fax: +44 2380 796965
cedwards@soton.ac.uk

Systemic lupus erythematosus (SLE) is an auto-immune connective tissue disorder with diverse clinical presentations owing to the involvement of multiple organs and tissues in the disease process. The underlying cause of SLE remains to be defined but genetic and environmental factors are both recognized to play a role. SLE-related genes have been identified from three clear sub-networks. These involve complement-related molecules, interacting with Fc-γ receptors, with the NF-κB complex and IL-10 [1]. There is also evidence for the importance of epigenetic factors through altered miRNA regulation, with one trial showing different expressed miRNAs in patients of African (African–American) versus European origin (European–American) with lupus nephritis [2].

Patients from an African or Asian background living in industrialized countries appear to have the highest prevalence of SLE. This is thought to be owing to genetic factors and environmental triggers, such as smoking or viral infections [1]. Previous reviews have found that the risk of developing SLE is increased in certain ethnic groups such as those of Hispanic and African or Asian background [3,4]. These patients develop SLE at an earlier age, and have more active disease [5]. These groups may have more renal or neurological manifestations [6]. Patients of different racial origins also have a high variability in the phenotypic expression, course of their disease and response to therapy. Higher mortality rates have been noted among groups with African, Hispanic and First Nation groups. This

review will examine the evidence for variations in treatment response in individuals with SLE from different racial backgrounds.

SLE in different racial groups
■ Incidence & prevalence rates

The incidence and prevalence of SLE appears to be lower in Europeans and their descendants when compared with other racial groups. Several studies have shown that incidence and prevalence rates for SLE are approximately two- to three-times higher in people of African or Asian background than in European populations [7–10]. Data from Hong Kong, with a 95% ethnic Chinese population, has shown prevalence rates to be intermediate between those of European and African origin (African–Americans) [11]. The disease also appears to be more common among Aboriginal than non-Aboriginal Australians [12], and in some First Nation or Native American groups in Canada [13]. Interestingly, the disease is reported to be rare in Africa, but common in people of African descent. A study of women who had recently migrated from West Africa to London reported that the prevalence of lupus was much higher in this group than in Europeans, but slightly lower than Afro–Caribbean women, suggesting either an important role for genetic factors or sudden changes in environmental exposures (perhaps reduced infectious exposure in London compared with Africa) [14]. Taken together, the majority of current evidence suggests that Europeans and their descendants in various parts of the world have a lower SLE

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incidence rates than ethnic groups from Asian and African backgrounds.

Phenotypic variation

The severity of clinical manifestations, including organ involvement and degree of disease activity also vary between patients with SLE from different racial backgrounds. Lupus nephritis is more prevalent in patients with African and Hispanic ancestry, as well as Chinese and other Asians compared with Europeans [15–20]. Furthermore, in multiethnic cohorts from the USA, Latin America, the UK and France, being of African or Latin American descent has consistently been identified as an independent risk factor for renal involvement and more rapid development of lupus nephritis [21–25]. Dramatic differences in prevalence according to race have been shown in biopsy-proven lupus nephritis with an increasing rate, respectively, from European to Asian, African and Chinese populations [19]. According to one study Asian patients, as well as those of African (Afro–Caribbean) descent, had higher neuropsychiatric complications as well as overall damage scores, when compared with Europeans [26]. Patients with an African origin are more commonly affected by discoid lupus than those of European descent, who appear more likely to develop photosensitivity or a malar rash [27]. There is also a documented phenotypic difference in SLE patients from Puerto Rico, who exhibit cutaneous manifestations much more frequently, but show less systemic disease activity, less damage and a substantially lower frequency of renal and neurological involvement when compared with Hispanics of predominantly Mexican ancestry [28].

Variations in autoantibody profile

Racial differences in autoantibody profiles have also been described in patients with SLE. While there appears to be no difference in prevalence of antinuclear antibody and anti-dsDNA antibodies, anti-Ro antibodies are more common in southern Chinese and north African populations. There also appears to be an increased prevalence of anti-Sm antibodies amongst African–Americans, north Africans, south Africans, Saudi Arabians and Vietnamese, whilst antiribosomal-P antibodies are more commonly seen in Japanese and Malaysian–Chinese populations [15,29].

Treatment of SLE

New ACR guidelines for the treatment of lupus nephritis have recently been published in which racial group, for the first time, influences treatment choice. We have examined the papers that informed the ACR guidelines and also reviewed subsequently published articles related to this topic.

As we have described, the risk of developing SLE, the clinical manifestations, autoantibody profile and severity of disease all vary between patients from different racial backgrounds. Differences in treatment response have also been reported across patients of different racial origins, which may impact on the choice of therapy for a given patient. These variations in treatment response and how this might alter prescribing among certain cohorts will now be considered for each medication in turn.

Problems with interpreting studies that compare treatment response in lupus patients from different racial groups

Comparing studies that report differences in treatment response for different ethnic groups can be challenging. This is owing to the often subjective and changing nature of racial identification. The relationship between race, ethnicity and geographical region is complex and designations of race and ethnicity are often arbitrary and heterogeneous. The Office for National Statistics in the UK recognizes that various possible ways of measuring ethnic groups are available and have been used over time. These include country of birth, nationality, language spoken at home, skin color, national/geographical origin and religion. US FDA guidelines for the 'Collection of race and ethnicity data in clinical trials', recommend that participants self-report their racial and ethnic ancestral origins.

In addition, studies showing differences in response to treatments in lupus patients from different racial groups are often based on *post hoc* analysis of trials powered to need the full complement of patients from all racial groups. For this reason some care is needed.

Racial differences in response to therapy for lupus

There appear to have been no major differences in the response to corticosteroids, hydroxychloroquine and azathioprine (AZA), used to treat lupus in different racial groups. Although no specific trials have been designed, these medications have been shown to be efficacious in trials in which all major racial groups were represented. Hydroxychloroquine has a broad spectrum of beneficial effects, including prevention of lupus flares and increase in long-term

survival of patients with SLE. It is recommended that it be given to patients with SLE during the whole course of the disease irrespective of racial background [30–32].

■ Agents used as induction therapy for lupus nephritis
Cyclophosphamide

Cyclophosphamide (CYC) has been used for over 30 years to treat patients with lupus nephritis. Since the first use, many studies have provided data showing reduced mortality, early response and remission, induction and flare prevention. The adverse reaction profile, effects on fertility and difference in response among patients with different racial origin has also been studied.

The NIH trials compared combination therapy (i.e., pulsed CYC with methylprednisolone) with methylprednisolone alone for the treatment of lupus nephritis. These showed that high-dose intravenous CYC (500–1000 mg/m^2 body surface area given every month for 6 months) led to better outcomes with respect to renal failure and was superior in preventing treatment failure than methylprednisolone alone [33–35]. They did not include effect of race in primary or secondary end points, and groups were similar in terms of race, gender and age.

Subsequently, Dooley et al. reported that for treatment of SLE with diffuse proliferative glomerulonephritis, intravenous CYC once monthly for 6 months at a dose of 500–1000 mg/m^2 with subsequent three monthly intravenous CYC and corticosteroids (oral prednisone was recommended at a starting dose of 60 mg per day for 2 months, and tapered as required for individual patients or methylprednisolone at a dose of 7 mg/kg per day for 3 days), was less effective in patients from an African background compared with other racial groups [36]. The differences in renal survival curves between racial groups up to 5 years were significantly worse for patient from an African origin than for other racial groups (p = 0.007). Renal survival estimates for other racial groups was 94.5% at 9 months and at 5 years. Renal survival at 9 months for those of African origin was 85%, and it declined over the 5 years with renal survival of 57% at 5 years. In the group of patients from an African background who rapidly progressed to end-stage renal disease, there were no differences in clinical, laboratory or pathologic features when compared with other patients; the cumulative dose and duration of immunosuppressives were lower in patients from an African background (owing to discontinuation following development of

end-stage renal disease). The socioeconomic status of participants was not known.

In the ELNT trial, the efficacy of low-dose versus high-dose intravenous CYC therapy as induction therapy for lupus nephritis was compared in SLE patients. The results suggested a more favorable outcome with fewer adverse events in the low-dose group (six pulses of intravenous CYC every 2 weeks at a fixed dose of 500 mg) [37]. There were 80.4% European, 8.7% Asian and 10.9% African origin in the high-dose CYC group versus 88.6% European, 4.5% Asian and 6.8% African origin in the low-dose CYC group. After 10 years of follow-up, death, sustained doubling of serum creatinine and end-stage renal disease rates were not significantly different between patients receiving high- and low-dose CYC [38]. This trial did not specifically include race as primary or secondary end points. Patients were randomized by minimization. The authors did not quote ethnicity as a determinant in the minimization. However, there were fewer patients from an African background included in the ELNT trial (9% of the cohort) compared with 23–43% reported in NIH studies. This difference in representation of racial groups is recognized as a factor that could influence the generalizability of these results, as the outcome of lupus nephritis is poorer in patients from an African than a European background.

Mycophenolate mofetil

CYC and mycophenolate mofetil (MMF) have been compared in randomized controlled trials (RCTs) of induction therapy for lupus nephritis [39,40]. Chan et al. described the use of MMF in place of CYC for induction of remission and maintenance treatment. Their major study compared MMF (2000 mg/day for 6 months followed by 1000 mg/day for 6 months) with oral CYC (2.5 mg/kg/day for 6 months) followed by AZA (1.5 mg/kg/day for 6 months) [41]. Long-term follow-up of these patients showed that the MMF-based induction/maintenance regimen had comparable long-term efficacy in terms of renal preservation and the prevention of relapse, to the sequential CYC and AZA regimen, but was associated with a significant reduction in adverse events, in particular infections and amenorrhea were reduced [39]. In this study, 100% of the cohort was Chinese (Hong Kong), which limits the generalizability of these findings to other racial groups.

Other studies using MMF have included populations with different racial mixes. Ginzler et al. compared MMF (initial dosage of 1000 mg/day,

increased to 3000 mg/day) with intravenous monthly CYC (500–1000 mg/m^2) in a randomized open-label noninferiority trial and concluded that induction therapy with MMF was superior to intravenous CYC in inducing complete remission of lupus nephritis [40]. In this study, 56% of the patients reported their race as black, 17% Caucasian, 20% Hispanic, 6% Asian and 1% were of other race or ethnic group. The patients were enrolled in the USA, and black and Hispanic patients made up 76% of the cohort. The study was powered to show noninferiority of MMF but not powered to examine differences in race, region or ethnicity. The effect of race was not included in the planned statistical analysis described in the methods section. However, there was a suggestion in the discussion that MMF may be more effective in those of African origin (African–American). Previous studies have highlighted the fact that higher doses of MMF are needed for African–American renal transplant patients [42].

The ALMS study (double-blinded RCT) was established to examine the efficacy and safety of MMF compared with intravenous CYC when administered with corticosteroids as induction therapy for patients with active lupus nephritis. The protocol was designed to standardize the management of lupus nephritis across all geographical regions. Patients were from a diverse range of racial and ethnic groups and locations worldwide. Out of a total of 370 patients, 39.7% of patients reported their race as Caucasian, 33.2% as Asian, 12.4% as black and 14.6% as other. The patients were enrolled in 20 countries in Asia, Australia, Europe, Latin America, USA and Canada. Overall, there was no difference between the two treatment groups with respect to median time to 50% reduction in proteinuria and also the incidence of adverse events was comparable between the two treatment groups. The results from additional *post hoc* analyses of the efficacy and safety data suggested that race, ethnicity and geographical region influence response to therapy. More patients from the black and Hispanic ethnic groups responded to MMF compared with intravenous CYC (53.9 vs 40% and 60.9 vs 38.8%, respectively). Response rates to both agents were similar in Asian and Caucasian groups. More patients in the black group receiving intravenous CYC were likely to withdraw prematurely due to adverse events (38.9%) compared with other racial groups: Caucasian (2.8%), Asian (5.0%). There was also a difference in treatment withdrawal between agents; more patients from the black group withdrew from intravenous CYC

(38.9%) than MMF (7.7%) treatment. By contrast, more patients in the Asian group receiving MMF withdrew owing to adverse events (22.6%) compared with those receiving intravenous CYC (5.0%). Possible reasons for these observations might be differences in prognostic and socio-economic factors, education, access to medical care within a geographical region, variations in treatment tolerability and differences in how subgroups metabolize the respective drugs. However, the trial was not powered to detect an effect of a specific region, race or ethnicity, which limits the significance of these findings [43,44]. Of note the racial group analysis was a *post hoc* review of the main study. The combined black/other group was separated for the purposes of this. The main studies of MMF versus CYC in induction therapy used are summarized in Table 1.

■ **Agents used for maintenance therapy in lupus nephritis**
MMF & AZA
MMF and AZA are often used for maintenance therapy in patients with SLE. The MAINTAIN lupus nephritis trial was designed to assess potential superiority of one of these agents in maintaining patients who have responded to initial induction therapy. A total of 105 patients received six intravenous CYC 500 mg fortnightly and subsequently were randomized to AZA (target dose of 2 mg/kg/day) or MMF (target dose 2000 mg/day). All patients were recruited by European centers. In the AZA group, 78.8% of patients were European, 7.7% were Asian and 13.5% were of African origin; with 79.2%, 9.4%, 11.3% in the MMF group, respectively. In this predominantly European cohort, there was no statistically significant difference between the agents; however, fewer renal flares were observed in the MMF group [45].

The ALMS study also compared MMF with AZA for maintenance therapy for lupus nephritis. The patients who met response criteria during the induction phase of the ALMS study were randomized either to MMF (2000 mg/day) or to AZA (2 mg/kg/day). Out of 227 patients, 72 were enrolled in Asia, 60 in Latin America, 47 in North America, 40 in Europe, five in south Africa and three in Australia. In the AZA group, 45.9% patients reported their race as Caucasian, 33.3% as Asian, 9.9% as black and 10.8% as other, with 41.4, 33.6, 10.3 and 14.7% in MMF group, respectively. Irrespective of race or geographical area MMF was found to be superior to AZA in maintaining the renal response and in preventing relapse in patients

Table 1. Induction therapy: cyclophosphamide versus mycophenolate mofetil.						
Study (year)	Type	Inclusion	Population	Intervention	OR	Ref.
Dooley et al. (1997)	Cohort Prospective	Renal biopsy-proven SLE-DPGN4 1982 ACR criteria for classification of SLE	51 black Americans 38 nonblack Americans	Intravenous CYC (NIH protocol)	Renal survival at 5 years 0.077 in black vs nonblack individuals	[36]
Houssiau et al. (2002), ELNT trial	Minimized Unblinded	Biopsy-proven lupus glomerulonephritis ACR criteria for SLE Previous CYC/AZA excluded	90 patients (76 Caucasian, six Asian and eight Afro–Caribbean)	Low-dose CYC (six pulses 500 mg) vs high-dose CYC (eight pulses, dose uptitrated to a maximum of 1500 mg)	Low-dose regimen comparable results to high dose No ethnicity analysis	[37]
Chan et al. (2005)	Randomized Unblinded	DPGN (WHO class IV) ACR 1982 criteria for SLE	62 patients	MMF Oral CYC (induction) AZA (remission)	MMF regime effective for continuous induction and maintenance No ethnicity analysis	[39]
Ginzler et al. (2005)	Randomized Unblinded Noninferiority 24-week duration	Four of ACR criteria for SLE Biopsy-proven LN class III or above Clinical activity (renal or serologic abnormality)	140 patients: – MMF group: 43 black, 12 Caucasian, ten Hispanic and six Asian – CYC group: 36 black, 12 Caucasian, 18 Hispanic and two Asian	MMF Intravenous CYC	MMF more effective than intravenous CYC for inducing remission No ethnicity analysis	[40]
Chan et al. (2000)	Randomized Unblinded 12-month duration	ACR criteria for SLE Biopsy-proven DPGN class IV	42 patients	MMF Oral CYC	MMF as effective as CYC followed by AZA No ethnicity analysis	[41]
Isenberg et al. (2010), ALMS study	Randomized Unblinded 24-week duration	ACR criteria for SLE Biopsy-proven LN class III–IV Active or active/chronic lesions	370 patients: – 39.7% Caucasian – 33.2% Asian – 12.4% black – 14.6% other (7.6% Mexican–Mestizo, 2.4% mixed, 0.8% Hispanic and 3.8% unclassifiable)	MMF Intravenous CYC	Similar response to MMF vs CYC in Asian and Caucasian groups MMF: – Black/other: 2.4 – Hispanic: 2.5 – Latin American: 3.4 MMF not superior to CYC overall	[43]
Appel et al. (2009)	24 weeks	SLE diagnosed by ACR criteria Biopsy-proven LN class III, IV and V	370 patients: – 39.7% Caucasian – 33.2% Asian – 27% other	MMF Intravenous CYC	CYC not as effective on non-Caucasian groups compared with MMF MMF vs CYC: – Asian: 0.6 – Caucasian: 1.1 – Other: 2.4	[44]

AZA: Azathioprine; CYC: Cyclophosphamide; DPGN: Diffuse proliferative glomerulonephritis; LN: Lupus nephritis; MMF: Mycophenolate mofetil; OR: Odds ratio; SLE: Systemic lupus erythematosus.

with active lupus nephritis [46]. Race and region was included as *post hoc* analyses. Subgroup analysis in the ALMS study showed that there was no significant difference in outcomes for individuals from different ethnic groups. However, there was a trend suggesting that black patients (only 23 patients) responded better to MMF as maintenance therapy. These studies are summarized in TABLE 2.

■ Biologic therapy in SLE
Rituximab
Many lupus patients do not respond to first-line therapies and experience relapses after initial clinical remission. Rituximab (RTX) is a chimeric antibody against CD20, a surface antigen expressed by B cells. It has been suggested that B cells contribute to SLE pathogenesis through the production of autoantibodies. RTX has been

Table 2. Maintenance therapy: mycophenolate mofetil versus azathioprine.

Study (year)	Type	Inclusion	Population	Intervention	OR	Ref.
Houssiau *et al.* (2010), MAINTAIN trial	Randomized 14-month follow-up	ACR criteria for SLE Biopsy-proven LN class III, IV, Vc or Vd	105 patients	CYC induction: – AZA – MMF	No statistically significant difference No ethnicity analysis	[45]
Dooley *et al.* (2011)	Randomized Double-blind Double-dummy 36-month follow-up	Biopsy-proven class III, IV or V LN Clinical response in induction to oral MMF or intravenous CYC (24 weeks)	227 patients: – 99 Caucasian – 23 black – 76 Asian – 29 other	MMF 1 g twice daily 2 mg/kg/day	MMF superior to AZA for maintenance No ethnicity analysis	[46]

AZA: Azathioprine; CYC: Cyclophosphamide; LN: Lupus nephritis; MMF: Mycophenolate mofetil; OR: Odds ratio; SLE: Systemic lupus erythematosus.

used to treat severe cases of lupus since 2002. There are multiple case reports and some observational studies available on the use of RTX that have shown high efficacy or even reduction or withdrawal of corticosteroids and an acceptable rate of adverse events [47,48].

The efficacy and safety of RTX was examined in the EXPLORER trial in which 257 patients were randomized 2:1 to receive RTX plus prednisone or placebo plus prednisone in two infusions 15 days apart and then were retreated 6 months later with the same regimen. An African, Hispanic and Asian background was present in 27.3, 9.1 and 5.7% of placebo-treated patients and in 23.7, 14.2 and 3.6% of RTX-treated patients, respectively. A total of 56.2% of the RTX group and 55.7% of the placebo group were Caucasian. All patients were enrolled from North American centers. The study failed to meet any of the primary or secondary end points. However, in the African and Hispanic origin subgroup there was a significant difference (p = 0.04) in the number of patients who had a major and partial clinical response to treatment between the RTX and placebo groups. Major clinical response of 13.8 and 9.4% and partial clinical response of 20 and 6.3% was observed in RTX and placebo groups, respectively. There was no difference reported in major secondary end points in this subgroup. It was speculated that disease in these patients is more B-cell driven, or that B-cell depletion is less likely to stimulate other mechanisms that could confound the effects of RTX [49].

Similar findings were reported in the LUNAR trial, in which 144 patients were randomized 1:1 to RTX or placebo on days 1, 15, 168 and 182. Both groups were treated concomitantly with MMF and corticosteroids. The racial distributions in the RTX group: 26.4% of patients were European, 27.8% were African and 40.3% were

of Hispanic origin, and, in the placebo group: 36.1% of patients were European, 27.8% were African and 31.9% were of Hispanic origin. All patients enrolled were from the USA and Latin America. This study did not demonstrate a statistically significant difference between patients treated with RTX and or with placebo. However, it showed a tendency toward superior response in reducing proteinuria, improvement in renal function, and the need for rescue therapy, as well as significantly improved anti-dsDNA and complement levels as serologic markers of disease activity in the RTX group. In addition, 25% of patients withdrew from the placebo arm compared with 10% in the RTX arm. Prespecified subgroup analysis was performed of the overall renal response at week 52 by race and ethnicity. Although not statistically significant and owing to partial rather than complete remission, a better response appeared to be observed in patients of an African origin. Among patients of an African origin, 70.0% of those who received RTX had a response, compared with 45.0% of those who received placebo. For Hispanic patients, the response rates were 55.0% with RTX and 47.8% with placebo, and the response rates for those with a European origin were 52.6 and 50.0%, respectively [50].

In these RCTs, although underpowered for racial subgroups analysis, there appeared to be an emerging trend that patients from an African background had a better response to RTX. These data could be used to justify a RCT of RTX in a lupus nephritis cohort from an African background. The summary is presented in TABLE 3.

Belimumab

Belimumab is a fully human recombinant IgG1λ monoclonal antibody to soluble B-lymphocyte

stimulator. It is the first, and so far the only, biologic to show consistent efficacy when used to treat SLE in RCTs, and it is the first drug to be specifically approved for treating SLE in more than 50 years. To date, two large randomized, double-blind, placebo-controlled trials, BLISS-52 and BLISS-76 have been published [51,52]. Patients were randomized in a 1:1:1 ratio to receive 1 mg/kg belimumab 10 mg/kg belimumab or placebo intravenously on days 0, 14 and 28 and then every 28 days until 48 and 72 weeks, respectively. In BLISS-52, patients were enrolled in 13 countries; Latin America (Argentina, Brazil, Chile, Colombia and Peru), Asia–Pacific (Australia, Hong Kong, India, Korea, Philippines and Taiwan), and eastern Europe (Romania and Russia). Out of 865 patients, 32.5% were Native Americans, 26.5% of European, 3.5% of African, 37.8% of Asian and 48.6% of Hispanic or Latino racial origin. BLISS-76 enrolled patients from Europe and North/Central America. Out of 819 patients, 12.6% patients were Native Americans, 69.5% were European, 14.4% were African, 3.4% were Asian and 21.1% were of Hispanic racial origin. There was a small but statistically significant benefit in the primary outcome, the SLE Responder Index at 52 weeks in the 10 mg/kg treatment arm in both studies. In BLISS-76, the SLE Responder Index response rates were numerically higher with belimumab

Table 3. Relapse: rituximab versus belimumab.

Study (year)	Type	Inclusion	Population	Intervention	OR	Ref.
Merrill et al. EXPLORER trial (2010)	Randomized Double-blinded Placebo-controlled	Four of ACR criteria for SLE Positive ANA Active disease at screening BILAG A with one or more organ involvement or BILAG B with two or more organ systems involved	257 patients African–American, Hispanic or Asian in: – RTX group: 41.5% – Placebo group: 42.1%	Intravenous RTX 1000 mg given on two separate occasions 14 days apart Placebo	No difference between RTX and placebo No ethnicity analysis	[49]
Rovin et al. LUNAR trial (2012)	Randomized Double-blind Placebo-controlled	SLE according to ACR criteria ANA positive Class III or IV (± V) LN on biopsy	144 patients: – 45 Caucasian – 40 black – 52 Hispanic – Seven Asia–Pacific islanders	Placebo Intravenous RTX on days 1, 15, 168 and 182 All patients received MMF	Number of responders to rituximab according to race (OR): – Caucasian: 10 (1.11) – Black: 14 (2.85) – Hispanic: 14 (1.34)	[50]
Navarra et al. (2011)	Randomized Placebo-controlled Double-blinded 52-week follow-up	ACR criteria for SLE Active disease (SELENA–SLEDAI score of 6 or more) Positive ANA or dsDNA Patients with active LN excluded	867 patients: – 143 Asia–Pacific – 241 Latin America – 56 eastern Europe (geographical region)	Placebo Belimumab 1 mg/kg Belimumab 10 mg/kg	Reduction in four or more points in SELENA–SLEDAI: – Belimumab 1 mg/kg: 53% – Belimumab 10 mg/kg: 58% – Placebo: 46% No ethnicity analysis	[51]
Furie et al. (2011)	Randomized Placebo-controlled Double-blinded 52-week follow-up	ACR criteria for SLE SELENA–SLEDAI score of 6 or more Positive ANA or dsDNA Severe active LN excluded	826 patients: – 303 Native American – 569 Caucasian – 118 black/ African–American – 28 Asian – 173 Hispanic (patients were categorized in more than one group)	Placebo Belimumab 1 mg/kg Belimumab 10 mg/kg	No ethnicity analysis	[52]

ANA: Antinuclear antibody; BILAG: British Isles Lupus Assessment Group; LN: Lupus nephritis; MMF: Mycophenolate mofetil; OR: Odds ratio; RTX: Rituximab; SELENA: Safety of Estrogens in Lupus Erythematosus National Assessment; SLE: Systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

than with placebo at week 76, but the differences were not statistically significant. Although the numbers were too small to draw conclusions, and the difference was not significant, a *post hoc* subgroup analysis of SLE Responder Index responses in patients of African origin (African–Americans and patients of African heritage) appeared less than that in the placebo group.

◼ Possible mechanisms to explain ethnic differences in response to treatments

Differences in drug responses between individuals are well recognized and may be due to genetic or environmental differences. These genetic or environmental influences may also result in interethnic or intergeographic differences in drug response. There are inter-racial differences accounting for variations in pharmacokinetics of drugs. For example, in a recent study, patients from an African background (African–American) were found to have an approximately twofold higher level of a toxic CYC metabolite when compared with patients from a European origin [3]. Other studies looking into dose intensity and toxicity of CYC between different ethnic groups in breast cancer did not appear to postulate changes in regimen given depending on racial background [4,53].

There are also differences in the choice of antihypertensives used to treat lupus nephritis according to racial group. Previous trials have shown angiotensin-converting enzyme inhibitors to have a lesser efficacy in control of blood pressure compared with thiazide diuretics in combination with calcium channel blockers in patients with African ancestry [54]. This is reflected in national guidelines [101].

Conclusion

There is evidence that disease frequency, autoimmune profile, clinical presentation and overall prognosis vary among patients with SLE from different racial backgrounds. There are also suggestions that variations are present in the treatment response seen in patients with SLE from different racial groups and geographical locations. However, it is important to note that the majority of studies appear to have looked at race in *post hoc* analyses, or have not been powered specifically for subgroup analysis of this sort. As such great care needs to be taken when translating these findings to clinical practice.

If these racial differences in response are real, whether they are secondary to genetic differences or environmental changes such as socioeconomic status and availability of healthcare facilities is not fully understood. Socioeconomic status was described in some of the trials, but again, they were often underpowered to look at this in relation to ethnicity and response to treatment.

A concern of all comparisons of treatment response between lupus patients from different racial groups is that variation in response may just be owing to the different severity that is seen between these groups. For example, patients of African origin generally have more severe lupus and, thus, will have a worse response to therapy. However, not all studies have suggested a worse response for those of African origin. In fact, a better response has been suggested with MMF when treating patients of African origin for lupus nephritis. It is also worth looking to see if the severity of disease seen in different ethnic groups is the same in the clinical trials. In the studies of lupus nephritis treatment that we have described, patients appeared to be of similar severity, in other words, class III or IV nephritis. However, in other studies the severity of disease was variable. This could be a confounding factor in assessing effect of race on treatment response.

More studies are needed to explore the genetic variations between patients of different racial groups, in particular those genes that have been associated with the development of SLE.

Designations of race and ethnicity are often arbitrary and heterogeneous, in some studies it was specified to be self reported. This meant that racial groups were referred to with different terminology (e.g., blacks vs African–Americans, Latino vs Hispanic, and so on). making comparisons between different trials more difficult. Analysis of available information was based on prospectively planned studies to examine the efficacy and safety of the treatment for patients, who were from a diverse range of racial and ethnic groups and locations worldwide. Whether geographical location has an effect separate from race has not been addressed and would be difficult to study. There is a need to study large cohorts of lupus patients prospectively and to design the trials to be powered to detect an effect on race or ethnicity. It would allow the findings to be generalized to the larger population of patients with SLE and to improve the outcome of this condition among people of different ethnic groups.

Future perspective

SLE remains a potentially difficult and life-threatening condition to treat. Treatment

options that are tailored to the individual patient and take into account factors, such as racial origin are more likely, in theory, to be effective.

Geographical location may have guided treatment in the past, possibly evolving from local experience of the disease. However, with global movement and increasing ethnic diversity, racial origin is likely to be more reliable than actual location.

As more evidence comes to light, we expect individualized treatment plans to become the norm of care, and racial origin may be an important factor in choice of treatment for SLE. However, great care is needed in drawing conclusions from the studies currently available.

Executive summary

Background
- Patients of different racial groups with systemic lupus erythematosus (SLE) appear to have a high variability in the course of their disease and response to therapy.
- This review examines the evidence for these variations in treatment response.

SLE in different racial groups
- Europeans and their descendants in various parts of the world have a lower prevalence of SLE than racial groups from Asian and African backgrounds.
- The severity of clinical manifestations and autoantibody profile also vary between patients with SLE from different racial backgrounds.

Treatment of SLE
- No major differences have been described in the response of different racial groups to corticosteroids, hydroxychloroquine and azathioprine.

Induction therapy
- Cyclophosphamide may be less effective in patients of African origin. However, this could be due to more severe disease – that is, lupus nephritis.
- Mycophenolate mofetil appears to be more effective in patients of African origin (African–American).

Maintenance therapy
- There was no statistical difference between ethnic groups for mycophenolate mofetil or azathioprine.

Biologic therapy
- Studies suggest that patients of African origin may have a better response to rituximab.
- No statistical difference between response rates for ethnic groups treated with belimumab.

Conclusion
- Variations in the treatment response have been suggested in patients with SLE from different racial groups and geographical locations.
- However the majority of studies appear to have looked at race in *post hoc* analyses and need to be interpreted with care.
- There is a need for further large prospective studies that look at racial differences in the management of SLE. The underlying biological differences that might underlie any variation in treatment response should also be investigated.

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