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Systemic lupus erythematosus and neutropaenia: a hallmark of haematological manifestations

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ABSTRACT

Objective Systemic lupus is a chronic autoimmune disease characterised by its phenotypic heterogeneity. Neutropaenia is a frequent event in SLE occurring in 20%–40% of patients depending on the threshold value of neutrophil count. On a daily basis, the management of neutropaenia in SLE is difficult with several possible causes. Moreover, the infectious consequences of neutropaenia in SLE remain not well defined.

Methods 998 patients from the Lupus BioBank of the upper Rhein (LBBR), a large German and French cohort of patients with SLE, mostly of Caucasian origin (83%), were included in this study. Neutropaenia was considered when neutrophil count was below 1800×10^6/L. An additional analysis of detailed medical records was done for 65 LBBR patients with neutropaenia.

Results 208 patients with neutropaenia (21%) were compared with 779 SLE patients without neutropaenia. Neutropaenia in SLE was significantly associated with thrombocytopaenia (OR 4.11 (2.57–10.3)), lymphopaenia (OR 4.41 (2.51–11.5)) and low C3 (OR 1.91 (1.03–4.37)) in multivariate analysis. 65 representative patients with neutropaenia were analysed. Neutropaenia was moderate to severe in 38%, chronic in 31%, and both severe and chronic in 23% of cases. Moderate to severe and chronic neutropaenia were both associated with lymphopaenia and thrombopaenia. Chronic neutropaenia was also associated anti-Ro/SSA antibodies and moderate to severe neutropaenia with oral ulcers.

Conclusion This study is to date the largest cohort to describe neutropaenia in SLE. Neutropaenia displays a strong association with other cytopaenias, suggesting a common mechanism. Chronic neutropaenia is associated with anti-Ro/SSA antibodies with or without identified Sjögren's disease.

INTRODUCTION

SLE is a chronic autoimmune disease characterised by its phenotypic heterogeneity and a breakdown of self-tolerance with the production of pathogenic autoantibodies. The pathophysiology of SLE is influenced by both genetic predisposition and environmental factors.

Until recently, SLE has been viewed mainly as a disease resulting from T and B cell abnormalities. However, there is now evidence that the innate immune system is also critically involved and that it plays a central role in the initiation and perpetuation of autoimmunity in SLE. This occurs mainly through the production of type I interferons (IFN) by plasmacytoid dendritic cells, triggered by the activation of toll-like receptors by immune complexes.[1]

Neutrophils have been reported for many years as a potential source of autoantigens and inflammatory cytokines in SLE.[2] Enhanced neutrophil extracellular trap (NET) formation in SLE has been suggested to contribute to the disease by different ways, stimulating the production of type I IFNs from plasmacytoid dendritic cells and mediating endothelial dysfunctions and prothrombotic changes. NETosis and abnormal clearance of apoptotic bodies promote self-tolerance breakdown through the increased exposition of self-antigens, with autoantibody formation against post-translationally modified nuclear antigens.[3]

From the physician side, the most frequent abnormality involving neutrophils in SLE is neutropaenia. Neutropaenia was reported to occur in 20%–47% of patients depending on the threshold retained to define neutropaenia.[4–7] On a daily basis, the management of neutropaenia in patients with SLE is difficult as the physician should consider in detail and simultaneously disease activity but also ethnicity, drug toxicity, associated haematological pathologies and infections. On top, the bacterial infectious consequences of neutropaenia in SLE are not well defined.

Herein, we took advantage of a large multicentric European register LBBR (Lupus BioBank of the upper Rhein) to evaluate the prevalence of neutropaenia in Caucasian SLE and to identify correlations between neutropaenia and other SLE features (clinical, serological and biological or therapeutic factors), in order to define a phenotype of SLE patients with neutropaenia and to approach the underlying process behind. As a second step, we focused on two subgroups of patients with (1) chronic or (2) moderate to severe (<1000×10^6/L) neutropaenia to precise the influence of duration or severity of neutropaenia in the course of SLE.

METHODS

Study population

LBBR involves a European (German and French) network of 15 clinical departments localised in the upper Rhein valley. The LBBR study is a cross-sectional collection of detailed clinical and biological data (recorded on the day of inclusion in the study) from 1073 patients with SLE enrolled between August 2011 and October 2014. Among these variables, 47 were analysed in the present study. All clinical variables were recorded according to the whole medical history of the patient. Among the 1073 patients with SLE enrolled, 998 fulfilled the American College of Rheumatology (ACR) 1997 revised criteria for SLE. Patients' characteristics are given in all 998 patients. We lack information concerning neutropaenia for 11 patients. The statistical analysis for neutropaenia was made on the 987 patients left. The LBBR database was approved by the national data protection commission, *Commission Nationale Informatique et Liberté* (CNIL). Patients gave informed consent before inclusion.

Definition of neutropaenia, chronic neutropaenia and severe neutropaenia

Neutropaenia was defined by the presence of less than 1800×10^6/L neutrophils at least one time during the history of the patient.

A complementary study was done for 65 patients out of 208 SLE patients with neutropaenia, coming from two representative centres of the LBBR study. The medical records were retrospectively watched in terms of clinical events (infections, flares), biological parameters and evolution of neutropaenia according to disease activity and concomitant therapies. Especially, infections were recorded according to the medical history, the clinical and biological data available in the medical record, and according to self-reporting by the patient.

Patients included in the 'chronic neutropaenia' subgroup had less than 1500×10^6/L neutrophils in circulating blood for at least 6 months. Patients included in the 'moderate to severe neutropaenia' subgroup had less than 1000×10^6/L in circulating blood two or more times and with an interval of at least 1 month.

Statistical analysis

A univariate analysis was conducted to evaluate potential factors associated with neutropaenia, using χ^2 test for qualitative variables and Mann-Whitney test for quantitative variables. Then, variables with a p value <0.10 on univariate analysis and the criteria supposed to influence the number of neutrophils in SLE according to the literature were included in a multivariate model. Adjustment for multiple testing was performed with the Benjamini and Hochberg method. Statistical significance was set at p<0.05.

A similar approach was used for the subgroup analysis of patients with 'chronic neutropaenia' and 'moderate to severe neutropaenia'. All statistical analyses were performed using JMP V.13.

RESULTS

Patients' characteristics in the LBBR study

There were 1073 patients with SLE included in LBBR, including 998 patients (89% female) fulfilling the ACR 1997 revised criteria for SLE. Of the patients, 83% were Caucasian and the mean score on Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) on the day of inclusion was 4.1. The detailed characteristics of these 998 patients are shown in online supplementary table S1. Briefly, the mean age at inclusion in the study was 43.5 years old, with a disease onset between 20 and 39 for 56.4% of the patients. The main clinical features (from the ACR classification) were arthritis (71.2%), photosensitivity (62.9%) and malar rash (54.2%). Of the patients, 34% experienced renal disease associated with SLE and 17.4% had a familial history of autoimmune disease, including SLE for 7.9%. Regarding the biological parameters, 66% of the patients experienced cytopaenia, including 21% neutropaenia, 53.8% lymphopaenia and 17.8% thrombopaenia. Of the patients, 30% had a positive Coombs test. Almost all patients (98.2%) had ANA, including 77.3% anti-double-stranded DNA, 41.9% anti-Ro/SSA antibodies, 34.9% anti-nucleosomes and 15.5% anti-Smith antibodies. Complement (CH50) was low in 30.1% of the cases at the time of inclusion, with 47.3% of the patients having low C3 and 47.2% having low C4. Regarding therapeutics, hydroxychloroquine was the first therapy used in 91.8% of cases, followed by azathioprine (41.6%), mycophenolate mofetil (36.1%), cyclophosphamide (26.6%) and methotrexate (26%). Of the patients, 86.6% took steroids at the time of inclusion. Altogether these results are comparable with data issued from the main lupus cohorts.[8–10]

SLE patients with neutropaenia in the LBBR study

Of the patients, 208 experienced neutropaenia (21%) and 779 (78%) did not. We lack information for 11 patients (1%).

In univariate analysis, neutropaenia was significantly associated with thrombocytopaenia (OR 3.68 (2.58–5.25), p<0.0001), lymphopaenia (OR 3.34 (2.37–4.72), p<0.0001), low C3 (OR 1.83 (1.29–2.59), p=0.0006), low C4 (OR 1.62 (1.15–2.29), p=0.006) and positive Coombs test (OR 2.91 (1.96–4.32), p<0.0001).

Table 1 Multivariate analysis of variables associated with neutropaenia

Variables	Neutropaenia (n=208)	No neutropaenia (n=779)	Univariate		Multivariate	
			OR (95% CI)	P value*	OR (95% CI)	Adjusted p value†
Significant variables in univariate analysis						
Lymphopaenia, n (%)	157 (75.5)	373 (47.9)	**3.34 (2.37 to 4.72)**	**<0.0001**	**4.41 (2.51 to 11.5)**	**0.001**
Thrombocytopaenia, n (%)	73 (35.8)	102 (13.1)	**3.68 (2.58 to 5.25)**	**<0.0001**	**4.11 (2.57 to 10.3)**	**0.0006**
Low C3, n (%)	101 (59.1)	250 (44.1)	**1.83 (1.29 to 2.59)**	**0.0006**	**1.91 (1.03 to 4.37)**	**0.26**
Coombs test +, n (%)	67 (48.6)	116 (24.5)	**2.91 (1.96 to 4.32)**	**<0.0001**	1.29 (0.69 to 2.60)	0.9
Low C4, n (%)	96 (56.5)	249 (44.5)	**1.62 (1.15 to 2.29)**	**0.006**	1.09 (0.54 to 2.22)	0.99
Variables suggested to be associated with neutropaenia in SLE						
Oral ulcers, n (%)	51 (24.6)	207 (26.8)	0.89 (0.63 to 1.27)	0.53	1.28 (0.65 to 2.70)	0.84
Susceptibility to infections, n (%)	13 (7.6)	49 (8.5)	0.89 (0.47 to 1.68)	0.72	0.86 (0.24 to 2.65)	0.95
Anti-Ro/SSA antibodies, n (%)	75 (45.2)	209 (40.5)	1.21 (0.85 to 1.72)	0.29	1.28 (0.70 to 2.53)	0.80
Azathioprine, n (%)	76 (40)	280 (42.0)	0.92 (0.66 to 1.28)	0.63	0.90 (0.43 to 1.78)	0.92
Cyclophosphamide, n (%)	43 (24.2)	168 (27.2)	0.85 (0.58 to 1.26)	0.42	0.57 (0.23 to 1.16)	0.98
Methotrexate, n (%)	43 (24.6)	155 (26.2)	0.92 (0.62 to 1.35)	0.66	1.45 (0.66 to 3.50)	0.67
Mycophenolate mofetil, n (%)	67 (36.8)	237 (35.8)	1.05 (0.74 to 1.47)	0.79	0.85 (0.39 to 1.74)	0.96
Rituximab, n (%)	16 (9.2)	53 (9.2)	1.00 (0.56 to 1.80)	1.00	0.94 (0.27 to 2.95)	0.55

Comparison between patients with neutropaenia (n=208) and without neutropaenia (n=779) in multivariate analysis. Significant variables in univariate analysis and variables suggested to be associated with neutropaenia in SLE according to literature were included in multivariate analysis.
Values with p< 0.05 are indicated in bold.
*Difference between patients with and without neutropaenia using χ^2 test for qualitative variables and Mann-Whitney test for quantitative variables.
†Adjustment for multiple testing was performed with the Benjamini and Hochberg method.

Neutropaenia was not associated with susceptibility to infections (OR 0.89 (0.47–1.68), p=0.72). The use of immunosuppressive treatments was also not associated with neutropaenia.

In multivariate analysis, neutropaenia was associated with lymphopaenia (OR 4.41 (2.51–11.5), p<0.001) and thrombocytopaenia (OR 4.11 (2.57–10.3), p<0.001) (table 1 and online supplementary table S2).

Analysis of two subgroups of patients with neutropaenia: 'chronic' and 'moderate to severe'

Chronic neutropaenia and moderate to severe neutropaenia were identified in 38% and 31% of SLE patients with neutropaenia, respectively. Of them, 23% presented an overlap with both moderate to severe and chronic neutropaenia (figure 1).

We compared patients from the group with chronic neutropaenia with the group of SLE patients without neutropaenia, and patients from the group with moderate to severe neutropaenia with the same second group.

Chronic neutropaenia was statistically associated with thrombocytopaenia (OR 3.90 (1.67–13.3), p<0.05), lymphopaenia (OR 7.67 (2.44–87.5), p<0.001) and anti-Ro/SSA antibodies (OR 3.41 (1.46–12.9), p<0.05) in multivariate analysis (table 2A).

Moderate to severe neutropaenia was statistically associated with thrombocytopaenia (OR 5.50 (2.34–22.0), p<0.001), lymphopaenia (OR 5.82 (1.73–64,7), p<0.01) and oral ulcers (OR 2.95 (1.12–10.7), p<0.05) in multivariate analysis (table 2B).

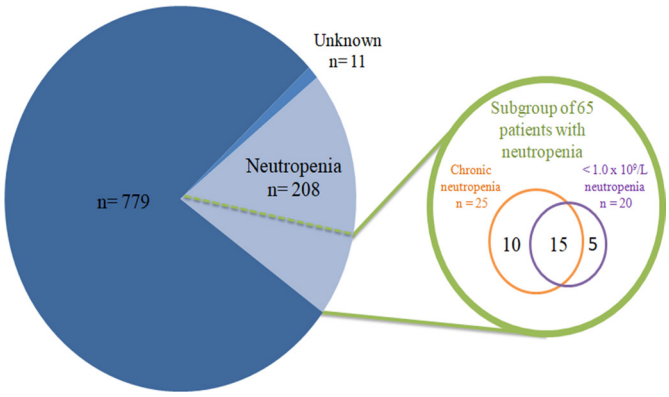

Figure 1 Graphical flow chart of the study.

DISCUSSION AND CONCLUSION

The LBBR cohort is a large and recent European study of patients with SLE. Nine hundred and ninety-eight patients responding to the ACR lupus criteria were included, with various forms and activity of SLE. Regarding the usual manifestations of the disease, patients enrolled in LBBR were representative of the diversity of SLE and comparable in many points with the other large cohorts of patients with SLE.[8–10] Most of the patients included in LBBR (83%) were of Caucasian origin, which is of importance regarding neutropaenia. Benign ethnic

Table 2 Multivariate analysis of variables associated with chronic (A) and moderate to severe (B) neutropaenia

Variables	Chronic neutropaenia (n=25)	Without neutropaenia (n=779)	Univariate		Multivariate	
			OR (95% CI)	P value*	OR (95% CI)	Adjusted p value†
(A) Chronic (>6 months) neutropaenia						
Thrombocytopaenia, n (%)	11 (45.8)	102 (13.1)	5.59 (2.44 to 12.8)	**<0.0001**	3.90 (1.67 to 13.3)	**0.02**
Lymphopaenia, n (%)	23 (92.0)	373 (47.9)	12.5 (2.92 to 53.3)	**<0.0001**	7.67 (2.44 to 87.5)	**0.0007**
Anti-Ro/SSA antibodies, n (%)	16 (66.7)	209 (26.8)	2.94 (1.23 to 6.99)	**0.01**	3.41 (1.46 to 12.9)	**0.02**
Oral ulcers, n (%)	10 (40.0)	207 (26.7)	1.82 (0.81 to 4.12)	0.16	1.69 (0.63 to 5.06)	0.56
Variables	**Moderate to severe neutropaenia (n=20)**	**Without neutropaenia (n=779)**	**Univariate**		**Multivariate**	
			OR (95% CI)	**P value***	**OR (95% CI)**	**Adjusted p value†**
(B) Moderate to severe neutropaenia (<1.0×10^9/L)						
Thrombocytopaenia, n (%)	10 (52.6)	102 (13.1)	7.34 (2.91 to 18.5)	**<0.0001**	5.50 (2.34 to 22.0)	**0.005**
Lymphopaenia, n (%)	18 (90.0)	373 (47.9)	9.77 (2.25 to 42.4)	**0.0002**	5.82 (1.73 to 64.7)	**0.002**
Oral ulcers, n (%)	10 (50.0)	207 (26.8)	2.73 (1.12 to 6.66)	**0.02**	2.95 (1.12 to 10.7)	**0.04**
Anti-Ro/SSA antibodies, n (%)	10 (50.0)	209 (40.5)	1.47 (0.60 to 3.59)	0.40	1.65 (0.58 to 5.50)	0.90

(A) Comparison between patients with chronic neutropaenia (n=25) and without neutropaenia (n=779). Significant variables in multivariate analysis.
(B) Comparison between patients with moderate to severe neutropaenia (n=20) and without neutropaenia (n=779). Significant variables in multivariate analysis.
*Difference between patients with chronic neutropaenia or with moderate to severe neutropaenia and patients without neutropaenia using χ^2 test for qualitative variables and Mann-Whitney test for quantitative variables.
†Adjustment for multiple testing was performed with the Benjamini and Hochberg method.
–, variable not entered in the multivariate model.

neutropaenia is associated with Duffy null phenotype, present in a large majority of black people. Thirty per cent of black Americans and >90% of some populations in central Africa are homozygous for null alleles at the Dell blood group, which is expressed on red blood cells and white blood cells, and in addition is a receptor for *Plasmodium vivax* malaria.[11] The impact of ethnicity in our study is marginal, enabling other variables associated with neutropaenia to be highlighted.

This study is to date the largest cohort to describe the association of neutropaenia with other SLE features and outcomes.

Our results confirm that neutropaenia is not rare in the course of SLE, with a prevalence of 21%. We also describe that deeper neutropaenia with less than 1000×10^6/L neutrophils and chronic neutropaenia for more than 6 months are rather rare, as they only represent 23% of SLE patients with neutropaenia.

These results complete and clarify what was already reported in three previous studies of smaller size. Nossent and Swaak[4] reported an occurrence of neutropaenia of 47% at a rate of 2000/mm^3, but neutropaenia was severe (<1000×10^6/L) in only 6% among 126 patients with SLE. Beyan *et al*[5] reported a prevalence of 20% among 115 patients with SLE (<1800×10^6/L) and Dias *et al*[6] a prevalence of 40.3% among 124 patients with SLE, among which 0.8% had severe neutropaenia (<1000×10^6/L) and 4.8% had persistent neutropaenia.

Our study shows a strong association between neutropaenia and haematological features of SLE (especially thrombocytopaenia and lymphopaenia). These associations persist in the subgroup analysis of patients with chronic and moderate to severe neutropaenia. Neutropaenia was associated with a positive Coombs test in univariate analysis on the entire cohort but did not reach significance in multivariate analysis, probably due to missing data (missing in 38.5% of the cases in the global cohort). Thus, these observations suggest a common pathophysiological mechanism of these cytopaenias, possibly via B cell tolerance breakdown and antibody-mediated mechanisms.

SLE patients with chronic neutropaenia from the LBBR cohort present a strong association with anti-Ro/SSA antibodies positivity. This was already reported by Kurien *et al*,[12] who explained this link by a cross-reactivity of anti-Ro/SSA antibodies towards neutrophil's surface proteins, inducing the activation of complement cascade and cell destruction. In primary Sjögren's syndrome, neutropaenia is also associated with anti-Ro/SSA and anti-La/SSB antibodies. Furthermore, in neonatal lupus with passive transfer of maternal anti-Ro/SSA autoantibodies, a high incidence of neutropaenia is observed. In our cohort and the subgroups, neutropaenia was however not associated with secondary Sjögren's syndrome. Altogether, these observations could suggest a causal link between anti-SSA antibodies and neutropaenia beyond the existence of Sjögren's disease associated with SLE.

Haematological manifestations are commonly associated with the activity of SLE as they reflect a proinflammatory effect of SLE on bone marrow and survival of

peripheral cells.[7] In our study, neutropaenia, strongly associated with lymphopaenia, could represent a hallmark of patients with disease activity. Indeed, previous works highlighted a link between lymphopaenia and lupus activity and severity.[4 5 13] In parallel, complement consumption is also known to be associated with disease activity. In our study, low C3 and low C4 were found to be associated with neutropaenia in univariate analysis only. An association between decreased complement levels and haematological SLE activity has been previously described, but neutropaenia was not specifically studied.[14] Indeed, the SLEDAI was not statistically different between patients with and without neutropaenia (4.2 vs 4.9; p=0.65). However, we cannot state that neutropaenia is, or not, a marker of SLE activity, considering that SLEDAI parameters are recorded at the time of the inclusion and that neutropaenia is noticed as occurring during the anterior course of the disease.

Moderate to severe neutropaenia was associated with oral ulcers. This association could reflect the activity of the disease. It could also reflect the severity of neutropaenia at one point (responsible for ulcers in other conditions such as drug-induced neutropaenia) or translate a susceptibility to viral (eg, herpes) or bacterial infections, of which buccal localisation is often seen due to an important bacterial colonisation and common micro-traumatism.

The role of neutropaenia in the occurrence of infections in SLE has been debated.[6 15] No significant association was found between neutropaenia and susceptibility to infections within the LBBR cohort. We cannot dismiss the possibility that moderate and low severity infections have been neglected by physicians or the patient itself, inducing an under-reporting of non-severe infectious events. However, this observation was persistent in the subgroups of chronic and moderate to severe neutropaenia, although the numbers of patients were low. A focus should be done prospectively on patients with SLE with neutrophil counts below 1000×10^6/L or neutropaenia of more than 6 months to assess these points.

The design of LBBR did not enable us to know precisely if neutropaenia was concomitant with the use of one of the treatments or the presence of infection, and prospective studies remain needed. Moreover, we explored 65 out of 208 patients in two representative centres to explore the medical data of patients with moderate to severe and chronic neutropaenia. Thus, we cannot exclude a centre effect or ascertainment biases.

Altogether and even if neutropaenia is not stricto sensu a criteria for lupus classification (Systemic Lupus International Collaborating Clinics or ACR) or activity (SLEDAI), this study highlights the potential role of neutropaenia as a biomarker of SLE with haematological activity. It also confirms a potential pathophysiological link with anti-Ro/SSA antibodies, but seems to be reassuring in terms of infectious susceptibility.

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Contributors A-SK, REV and AG designed the study. AM, AG, GB, YD, ZA, BB, CF, PK, HML, NM-B, FM, J-LP, H-HP, AS, JS, LA, TM, REV and A-SK collected the data and performed the study analyses. AM, AG, YD and A-SK wrote the manuscript. All authors read and approved the final version of the manuscript.

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Patient consent for publication Not required.

Ethics approval The study complies with the Declaration of Helsinki and was approved by the appropriate medical ethical committees.

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REFERENCES

1 Banchereau R, Hong S, Cantarel B, *et al*. Personalized Immunomonitoring uncovers molecular networks that stratify lupus patients. *Cell* 2016;165:551–65.
2 Bennett L, Palucka AK, Arce E, *et al*. Interferon and granulopoiesis signatures in systemic lupus erythematosus blood. *J Exp Med* 2003;197:711–23.
3 Lindau D, Mussard J, Rabsteyn A, *et al*. Tlr9 independent interferon α production by neutrophils on NETosis in response to circulating chromatin, a key lupus autoantigen. *Ann Rheum Dis* 2014;73:2199–207.
4 Nossent JC, Swaak AJ. Prevalence and significance of haematological abnormalities in patients with systemic lupus erythematosus. *Q J Med* 1991;80:605–12.
5 Beyan E, Beyan C, Turan M. Hematological presentation in systemic lupus erythematosus and its relationship with disease activity. *Hematology* 2007;12:257–61.
6 Dias AMB, do Couto MCM, Duarte CCM, *et al*. White blood cell count abnormalities and infections in one-year follow-up of 124 patients with SLE. *Ann N Y Acad Sci* 2009;1173:103–7.
7 Miranda-Hernández D, Cruz-Reyes C, Monsebaiz-Mora C, *et al*. Active haematological manifestations of systemic lupus erythematosus lupus are associated with a high rate of in-hospital mortality. *Lupus* 2017;26:640–5.
8 Cervera R, Khamashta MA, Font J, *et al*. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. The European Working Party on systemic lupus erythematosus. *Medicine* 1993;72:113–24.
9 Wang F, Wang CL, Tan CT, *et al*. Systemic lupus erythematosus in Malaysia: a study of 539 patients and comparison of prevalence and disease expression in different racial and gender groups. *Lupus* 1997;6:248–53.
10 Pons-Estel BA, Catoggio LJ, Cardiel MH, *et al*. The GLADEL multinational Latin American prospective inception cohort of 1,214 patients with systemic lupus erythematosus: ethnic and disease heterogeneity among "Hispanics". *Medicine* 2004;83:1–17.
11 Atallah-Yunes SA, Ready A, Newburger PE. Benign ethnic neutropenia.. *Blood Rev* 2019;37:100586.
12 Kurien BT, Newland J, Paczkowski C, *et al*. Association of neutropenia in systemic lupus erythematosus (SLE) with anti-Ro and binding of an immunologically cross-reactive neutrophil membrane antigen. *Clin Exp Immunol* 2000;120:209–17.
13 Rivero SJ, Díaz-Jouanen E, Alarcón-Segovia D. Lymphopenia in systemic lupus erythematosus. Clinical, diagnostic, and prognostic significance. *Arthritis Rheum* 1978;21:295–305.
14 Ho A, Barr SG, Magder LS, *et al*. A decrease in complement is associated with increased renal and hematologic activity in patients with systemic lupus erythematosus. *Arthritis Rheum* 2001;44:2350–7.
15 Carli L, Tani C, Vagnani S, *et al*. Leukopenia, lymphopenia, and neutropenia in systemic lupus erythematosus: Prevalence and clinical impact--A systematic literature review. *Semin Arthritis Rheum* 2015;45:190–4.