

SHORT REPORT

Worse long-term renal outcome of lupus nephritis patients of African descent living in Europe

Antoine Enfrein ¹, Valérie Pirson,² Véronique Le Guern,³ Adexandre Karras,^{4,5} Farah Tamirou,^{2,6} Nathalie Costedoat-Chalumeau,³ Frederic Houssiau^{2,6}

To cite: Enfrein A, Pirson V, Le Guern V, *et al.* Worse long-term renal outcome of lupus nephritis patients of African descent living in Europe. *RMD Open* 2022;**8**:e002386. doi:10.1136/rmdopen-2022-002386

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/rmdopen-2022-002386>).

Received 8 June 2022
Accepted 5 October 2022

ABSTRACT

Introduction Prognosis of lupus nephritis (LN) among patients of African descent living in Europe has been understudied.

Methods In a retrospective study performed in two European university hospitals, we compared the prognosis of LN in patients of African descent or Caucasians. Remission was defined as a urine protein to creatinine (uP/C) ratio <0.5 g/g and a serum creatinine value <120% of baseline. Renal relapse was defined as the reappearance of a uP/C >1 g/g, leading to a repeat kidney biopsy and/or immunosuppressive treatment change. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate ≤60 mL/min/1.73 m². Adherence was retrospectively assessed through medical files and/or hydroxychloroquine level measurements.

Results 52 patients of African descent and 85 Caucasian patients were included in this analysis. Class III and isolated class V LN were more common among patients of African descent. Time to first renal remission did not differ between ethnic subgroups. By contrast, patients of African descent suffered from earlier renal flares, CKD was more common and time to CKD was shorter after a flare. In a multivariate analysis, African ancestry was an independent risk factor for progression to CKD. We observed no significant difference in non-adherence to treatment between the two groups.

Conclusion LN patients of African descent have worse renal outcomes, mainly explained by a higher rate of renal flare.

INTRODUCTION

Renal involvement remains a major disease burden in systemic lupus erythematosus (SLE) leading to chronic kidney disease (CKD) in 30% of patients at 5 years with 10% of end-stage kidney disease (ESKD) at 10 years.¹

In SLE patients of African descent, lupus nephritis (LN) is considered to be more common and more severe, leading more frequently to ESKD or death.^{2–6} Of note, these conclusions mostly rely on American cohorts, where restricted access to the healthcare

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In the USA, lupus nephritis (LN) is more severe among patients of African descent, but whether this is true for patients living in Europe, where access to care is easier, is poorly studied.

WHAT THIS STUDY ADDS

⇒ We demonstrate that LN patients of African descent living in Europe exhibit worse renal outcomes, mainly due to higher risk of flares.
⇒ Despite similar remission rates after initial treatment, subsequent renal flares are more frequent and lead more often to chronic kidney disease in patients of African descent.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ European patients of African descent should be closely followed up after an episode of LN as they have a higher risk of flares and progression to chronic kidney disease.

system might be an important confounding factor. In a recent study on LN long-term outcome by Petri *et al*, poor outcome of patients of African descent remained statistically significant after adjustment for education level, but this might not properly reflect inequities in access to care.³

In Europe, only one cohort study originating from the Netherlands confirmed that non-white SLE patients had a poorer renal outcome, with more frequent flares and evolution to ESKD, but no specific data were available on patients of African descent.⁷

In France and Belgium, as in many other European countries, a nationwide social insurance system allows general access to healthcare, thereby minimising the impact of socioeconomic factors on disease prognosis. Therefore, we sought to investigate long-term outcomes in LN patients of African descent living in Europe.



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Antoine Enfrein;
antoine.enfrein@chu-nantes.fr

Table 1 Baseline characteristics of lupus nephritis patients of African descent versus Caucasians

	African descent (n=52)	Caucasian (n=85)	P value
Age	31.7 (±12)	29.4 (±9.0)	0.16
Women	50 (96%)	75 (88%)	0.13
Diagnosis decade			
<2000	1 (2%)	19 (22%)	<0.001
2000–2010	13 (25%)	41 (48%)	
>2010	38 (73%)	25 (29%)	
Histological class			<0.001
III±V (N; %)	20 (38%)	18 (21%)	
IV±V (N; %)	19 (37%)	61 (72%)	
V only (N; %)	13 (25%)	6 (7%)	
Biology			
Anti-DNA antibodies	45 (87%)	56 (66%)	0.004
aPL antibodies	10 (19%)	14 (16%)	0.72
Initial immunosuppressive drug			<0.001
CYC (N; %)	19 (37%)	63 (74%)	
MMF (N; %)	25 (48%)	15 (17%)	
Others (N; %)	8 (15%)	7 (8%)	
Other drugs			
Intravenous MP (N; %)	28 (54%)	63 (74%)	0.01
HCQ (N; %)	41 (79%)	65 (77%)	0.7
Biological parameters			
Creatinine (mg/dL)	1.16 (±1.5)	1.01 (± 0.5)	0.39
eGFR (mL/min/1.73 m ²)	93.9 (±40)	95.0 (±41)	0.87
Serum C3 (g/L)	0.64 (±0.3)	0.62 (±0.3)	0.8
Serum C4 (g/L)	0.12 (0.1)	0.10 (0.05)	0.1
uP/C (g/g)	3.53 (±5.2)	3.27 (±2.7)	0.7

Unless stated otherwise, values are mean±SD. P value <0.05 was considered statistically significant.
uP/C, urine protein to creatinine ratio; aPL, anti-phospholipid; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; MP, methylprednisolone.

METHODS

Patients selection

We screened files of SLE patients of African descent followed at the UCLouvain academic hospital in Belgium. As we did in a previous work⁸, we selected patients who had a history of proteinuria >0.5 g/day and who underwent a kidney biopsy and selected those who had an incident LN with International Society of Nephrology/Renal Pathology Society (ISN/RPS) class III, IV and/or V histology. We excluded patients with a follow-up of <12 months, who had a previous history of LN or CKD or with insufficient data at baseline or during follow-up. As the number of patients of African descent retrieved was too small, we collaborated with Hôpital Cochin in Paris to retrieve additional patients of African descent using with the same inclusion/exclusion criteria (online supplemental figure 1).

We compared LN patients of African descent with Caucasian patients included in our previously reported long-term outcome incident cohort.⁸

Outcomes

Renal remission was defined by a urine protein to creatinine (uP/C) value <0.5 g/g (confirmed on at least two subsequent samples) combined with a serum creatinine value <120% of baseline, consistent with current KDIGO (Kidney Disease: Improving Global Outcomes) definition.⁹

Renal flare was pragmatically defined by an increase in proteinuria (uP/C >1 g/g) leading to a kidney biopsy showing a class III/IV or V with signs of activity and/or intensification of the immunosuppressive treatment. CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² according to CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula. ESKD was defined as eGFR <15 mL/min/1.73 m², requiring dialysis or renal transplantation.

We considered patients to be severely non-adherent when they completely discontinued medical follow-up for a significant period of time (at least 1 year), admitted that they were not taking their medications for several weeks or months, or when whole blood hydroxychloroquine (HCQ) level was <200 µg/L in at least one sample.^{10–12} We considered them partially adherent when they admitted frequent omissions of their treatment (ie, at least 2–3/week) or when we found at least two whole blood HCQ levels <500 µg/L.

Statistical analyses

Chi-square tests, Fischer's exact tests, unpaired t-tests and Mann-Whitney tests were performed as appropriate with GraphPad Prism V.5.0. Survival curves, drawn according to Kaplan-Meier method, were statistically tested by the log-rank test. Multivariate analysis was performed using a time-adjusted Cox regression proportional hazards model, performed with Jamovi V.2.0 software with ClinicoPath package. For this purpose, we included in the model factors already well known as risk factors for progression to CKD (ever or never achievement of renal remission, ever or never renal flare) and those that differed between two populations at baseline (ie, decade of diagnosis, histologic class at diagnosis, initial treatment by cyclophosphamide or mycophenolate mofetil, prescription of intravenous methylprednisolone (MP), positivity of anti-DNA antibodies), which could be potential confounding factors.

RESULTS

Baseline characteristics

Overall, 52 patients of African descent and 85 Caucasians patients were included and their baseline characteristics are shown in table 1. Initial disease severity based on standard renal parameters did not differ between the two groups. Isolated class V LN was significantly over-represented among patients of African descent (25% vs 7%, p=0.003), and mycophenolate mofetil was more frequently prescribed as initial immunosuppressant in this group (48% vs 17%, p<0.001). Median follow-up

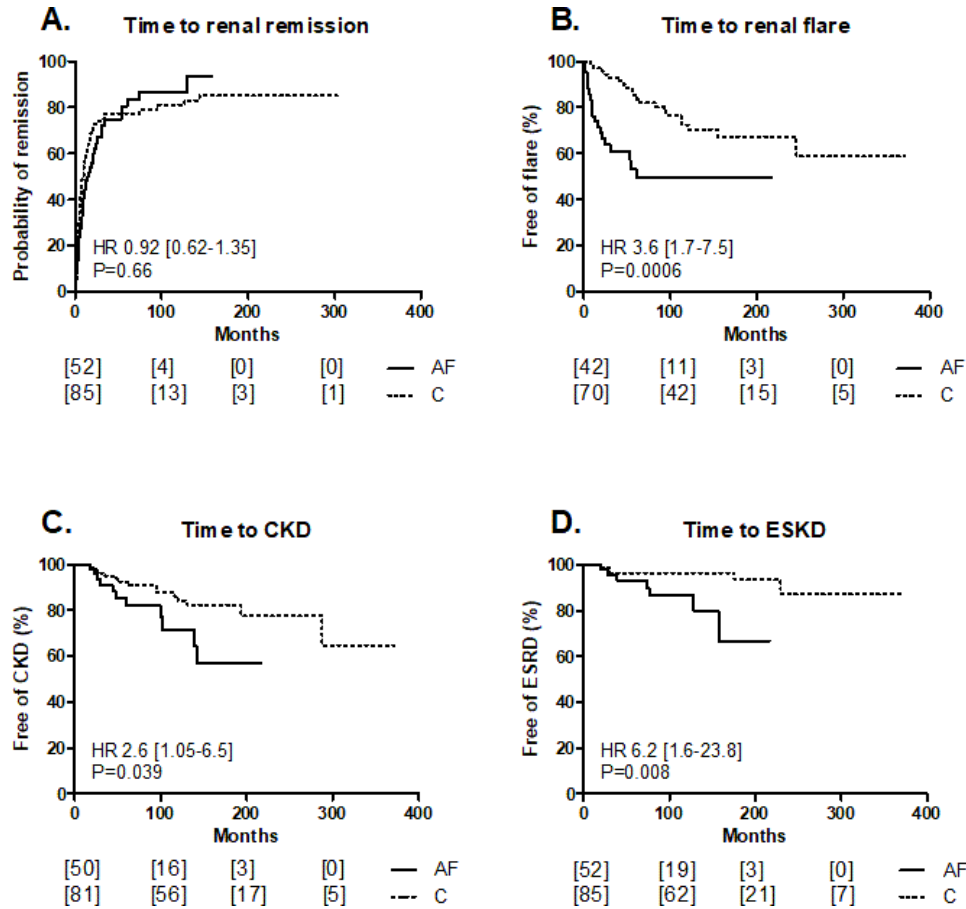


Figure 1 Kaplan-Meier analysis of (A) time to remission; (B) time to flare; (C) time to chronic kidney disease (CKD); (D) time to end-stage kidney disease (ESKD). Plain lines correspond to patients of African descent (AF) and dashed lines to Caucasians patients (C). Numbers between brackets along the abscissa indicate the number of patients at risk.

was significantly longer in Caucasians (148 vs 81 months, $p < 0.001$), and patients treated before 2000's were also over-represented in the Caucasian cohort (22% vs 2%, $p < 0.001$).

Renal outcome across ethnic groups

By Kaplan-Meier analyses, time to first renal remission did not differ between ethnic subgroups (figure 1A). By contrast, time to renal flare (figure 1B), to CKD (figure 1C) and to ESKD (figure 1D) was significantly shorter in patients of African descent compared with Caucasians.

Progression to CKD did not significantly differ between patients of African descent treated either with cyclophosphamide-based regimens or mycophenolate mofetil (HR 1.6; 95 CI (0.38 to 6.9); $p = 0.52$). There was also no difference for time to renal flare ($p = 0.158$).

In a multivariate analysis, we included variables known as prognostic factors for CKD (ever or never achievement of renal remission, ever or never renal flare) and baseline characteristics that differed between the two groups (decade of diagnosis, histologic class at diagnosis, initial treatment by cyclophosphamide or mycophenolate mofetil, prescription of intravenous MP, positivity of anti-DNA antibodies). Ethnicity and absence of remission

were the two independent risk factors for progression to CKD (HR 2.63, 95 CI (1.01 to 6.89), $p = 0.048$ and HR 70.60, 95 CI (14.18 to 351.45), $p < 0.001$, respectively; see online supplemental table).

Impact of absence of renal remission and of renal flares across ethnic groups

As depicted in figure 2A, time to CKD was shorter in patients who never achieved renal remission, irrespectively of their ethnic background. In the subgroup of patients achieving renal remission but further experiencing a flare, time to CKD was significantly shorter for patients of African descent (figure 2B). By contrast, time to CKD did not differ between patients from the two ethnic groups who never suffered from a renal relapse (figure 2C).

Adherence to treatment

Using definitions detailed supra, no significant difference in adherence to treatment could be unmasked between the two ethnic groups, with 15% and 48% of patients of African descent considered as partially adherent or non-adherent, respectively, versus 7% and 46% of Caucasians patients.

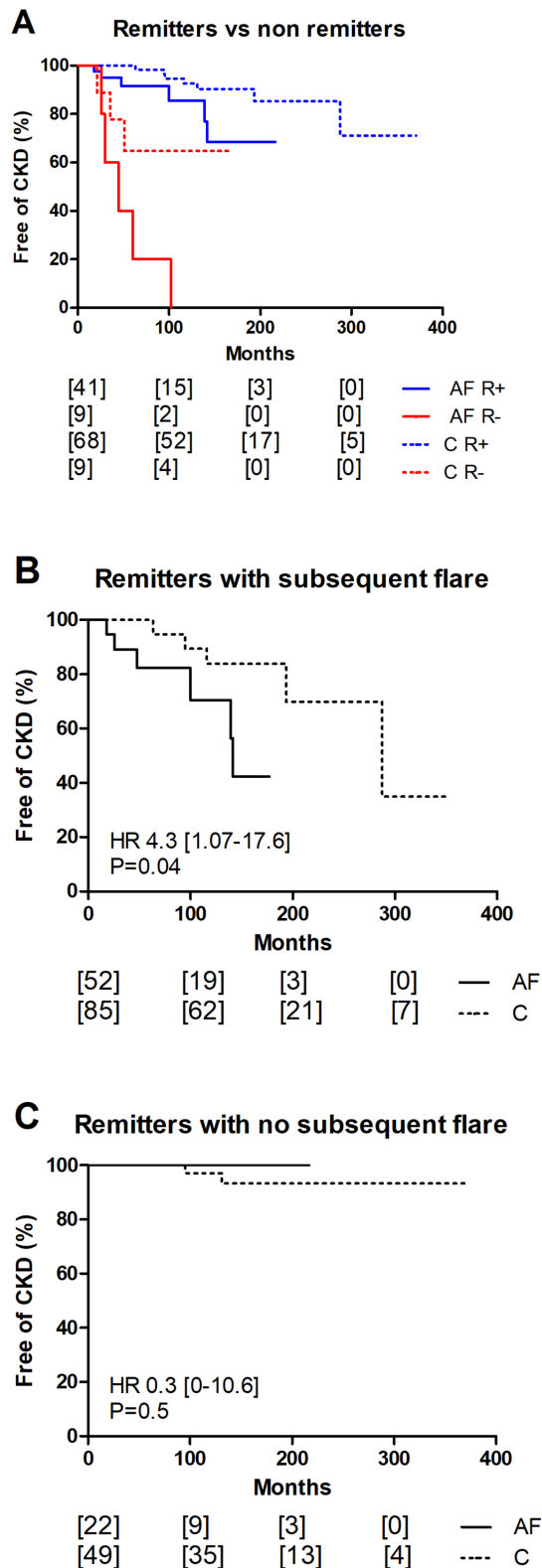


Figure 2 Kaplan-Meier analysis of progression to chronic kidney disease (CKD) among patients who (A) ever or never reached remission; (B) reached remission and had subsequent flares; (C) reached remission and had no subsequent flare. Plain lines correspond to patients of African descent (AF) and dashed lines to Caucasians patients (C). Blues lines correspond to remitters (R+) and red lines to non-remitters (R-). Numbers between brackets along the abscissa indicate the number of patients at risk.

DISCUSSION

Several US series have demonstrated that LN patients of African descent experience poorer outcomes than Caucasian patients (ref). Since access to the healthcare system in the US is not uniform and depends on wealthiness, socioeconomic factors introduce a bias in studies aimed at identifying long-term prognostic factors in LN across ethnic groups.

Here, we confirm a worse prognosis of LN in patients of African descent followed in two European university expert centres located in countries with generalised access to healthcare. Several hypotheses can be made to explain this difference.

First, early remission is known to be a key prognostic factor for CKD, but we did not observe a delayed kinetics to achieve remission among patients of African descent. This said, patients of African descent who did not achieve remission seem to have a catastrophic outcome, although the limited number of patients does not allow to draw robust conclusions and this should be confirmed in larger cohorts.

Second, this difference in outcome could be attributed to discrepancies observed between populations' characteristics at baseline. Thus, class VLN was over-represented among patients of African descent, as already described,¹³¹⁴ which is considered to expose patients to a lower risk of progression to CKD. Mycophenolate treatment as more commonly prescribed among LN patients of African descent. However, these two variables did not influence prognosis in a multivariate analysis. To strengthen our results, we also included in this multivariate analysis confounding factors inherent to methodological biases due to the retrospective nature of our study. Thus, neither diagnosis decade (patients treated before the 2000s were over-represented among Caucasians) nor intravenous MP treatment (over-represented among patients of African descent given intravenous PM as standard of care in the UCLouvain centre) nor immunosuppressive induction treatment predicted CKD in a multivariate analysis.

Third, we tested the hypothesis that the poor outcome among patients of African descent stemmed from the frequency and severity of flares. We show that flares are not only more common in patients of African descent (figure 1), as already reported for Maghrebian patients living in Belgium and France,¹⁵ but also that progression to CKD was more frequent after a flare (figure 2).

Our study has some limitations. First, we acknowledge that we might have introduced a bias by comparing Caucasian patients followed in one centre (Louvain) with patients of African descent followed in two departments (Louvain and Cochin), in order to increase the numbers of the second group. This said, analyses performed on patients followed only at Louvain revealed the same trend, with time to ESKD being shorter in patients of African descent ($p=0.056$). Second, we were not able to investigate *APOLI* distribution, a gene that encodes the trypanolytic L1 apolipoprotein and confers an increased risk of developing renal impairment

in African-Americans with various kidney diseases,¹⁶ including LN.¹⁷ *APOL1* genotyping was obviously beyond the scope of this retrospective analysis while its allele distribution is a likely contributor to the disease severity in European LN patients of African descent. Nonetheless, while such a mechanism might explain a higher rate of CKD, it does not support a higher risk of disease flare. Third, assessment of non-adherence in this retrospective series was limited to data available in the files and therefore likely inaccurate. HCQ measurements became routinely performed only over the last decade while many of our patients have a much longer follow-up. Using a very approximate estimate, we could not identify differences between the two ethnic subgroups. We suggest that this issue should be further investigated with an appropriate prospective methodology including iterative HCQ measurements, as non-adherence to therapy could explain a higher rate of flares among LN patients of African descent.

In conclusion, we confirm that patients of African descent leaving in Europe have a worse renal outcome compared with Caucasians. Renal flares seem a key explanation for more frequent progression to CK. Taken together, these observations are especially relevant given the shorter overall survival of patients of African descent once they have reached ESKD stage.⁶

Author affiliations

¹Service de médecine interne, CHU Nantes, Nantes, France

²Rheumatology, Cliniques universitaires Saint-Luc, Bruxelles, Belgium

³Département de Médecine Interne, Centre de Référence Maladies Auto-immunes et Systémiques Rares, Hôpital Cochin, Paris, Île-de-France, France

⁴Nephrology, Hôpital Européen Georges Pompidou, Paris, Île-de-France, France

⁵Université Paris Cité, Paris, France

⁶Institut de Recherche Expérimentale et Clinique, Pôle de pathologies rhumatismales systémiques et inflammatoires, Université catholique de Louvain, Bruxelles, Brussels, Belgium

Contributors AE and VP collected the data. AE did the statistical analyses. AE, FT, NC-C and FH contributed to the writing of the manuscript. All authors contributed to the follow-up of the patients.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants but was not approved by. According to French and Belgian laws, consent is not mandatory for retrospective observational studies.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines,

terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Antoine Enfrein <http://orcid.org/0000-0001-8844-9715>

REFERENCES

- Hanly JG, O’Keeffe AG, Su L, *et al*. The frequency and outcome of lupus nephritis: results from an international inception cohort study. *Rheumatology* 2016;55:252–62.
- Contreras G, Lenz O, Pardo V, *et al*. Outcomes in African Americans and Hispanics with lupus nephritis. *Kidney Int* 2006;69:1846–51.
- Petri M, Barr E, Magder LS. Risk of renal failure within 10 or 20 years of systemic lupus erythematosus diagnosis. *J Rheumatol* 2021;48:222–7.
- Korbet SM, Schwartz MM, Evans J, *et al*. Severe lupus nephritis: racial differences in presentation and outcome. *J Am Soc Nephrol* 2007;18:244–54.
- Austin HA, Boumpas DT, Vaughan EM, *et al*. Predicting renal outcomes in severe lupus nephritis: contributions of clinical and histologic data. *Kidney Int* 1994;45:544–50.
- Nee R, Martinez-Osorio J, Yuan CM, *et al*. Survival disparity of African American versus non-African American patients with ESRD due to SLE. *Am J Kidney Dis* 2015;66:630–7.
- Rijnink EC, Teng YKO, Wilhelmus S, *et al*. Clinical and histopathologic characteristics associated with renal outcomes in lupus nephritis. *Clin J Am Soc Nephrol* 2017;12:734–43.
- Pirson V, Enfrein A, Houssiau FA, *et al*. Absence of renal remission portends poor long-term kidney outcome in lupus nephritis. *Lupus Sci Med* 2021;8:e000533.
- Rovin BH, Adler SG, Barratt J, *et al*. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int* 2021;100:S1–276.
- Costedoat-Chalumeau N, Amoura Z, Hulot J-S, *et al*. Very low blood hydroxychloroquine concentration as an objective marker of poor adherence to treatment of systemic lupus erythematosus. *Ann Rheum Dis* 2007;66:821–4.
- Costedoat-Chalumeau N, Houssiau F, Izmirly P, *et al*. A prospective international study on adherence to treatment in 305 patients with flaring SLE: assessment by drug levels and self-administered questionnaires. *Clin Pharmacol Ther* 2019;106:374–82.
- Blanchet B, Jallouli M, Allard M, *et al*. Hydroxychloroquine levels in patients with systemic lupus erythematosus: whole blood is preferable but serum levels also detect non-adherence. *Arthritis Res Ther* 2020;22:223.
- Mody PG, Mody GM, Assounga A. The clinical manifestations and response to treatment in South Africans with lupus nephritis. *Lupus* 2018;27:1207–17.
- Bhinder S, Singh A, Majithia V. Membranous (class V) renal disease in systemic lupus erythematosus may be more common than previously reported: results of a 6-year retrospective analysis. *Am J Med Sci* 2010;339:230–2.
- Tamirou F, Costedoat-Chalumeau N, Medkouri G, *et al*. Disease severity of proliferative lupus nephritis in Maghrebians. *Lupus* 2018;27:1387–92.
- Foster MC, Coresh J, Fornage M, *et al*. *APOL1* variants associate with increased risk of CKD among African Americans. *J Am Soc Nephrol* 2013;24:1484–91.
- Freedman BI, Langefeld CD, Andringa KK. End-Stage Renal Disease in African Americans With Lupus Nephritis Is Associated With *APOL1*: *APOL1* in Lupus Nephritis ESRD. *Arthritis Rheumatol* 2014;66:390–6.