Protective effects of antimalarials in Chinese patients with systemic lupus erythematosus

We read with great interest the article by Müller-Calleja *et al*¹ in which a novel mechanism of hydroxychloroquine (HCQ) was discovered, which might explain well-established anti-inflammatory effects of antimalarials.^{2–4} HCQ and chloroquine (CQ), both known as antimalarial drugs, have become fundamental therapeutic elements in systemic lupus erythematosus (SLE) in these decades. However, their specific benefits on organ involvement and long-term outcome remain to be elucidated.

To examine the role of antimalarials in different clinical aspects of Chinese patients with SLE, we retrieved the medical records of 1372 patients with SLE who experienced their first hospitalisation at 26 centres across Jiangsu, an eastern province of China, between January 1999 and December 2009 from a longitudinal SLE database collected by the Jiangsu Lupus Collaborative Group.⁵ Demographics of the enrolled patients are summarised in table 1. All the patients were followed up in 2015 to check for their survival status. Based on Kaplan-Meier survival analysis, the

survival proportions for antimalarial users were 92.6%, 90.3% and 87.8% at 5, 10 and 16 years, significantly higher than that of non-users (83.1%, 78.9% and 76.0%, $p=0.000$) (figure 1A), which was consistent with previous reports in Latin American, African-American and Caucasian patients with SLE.^{6–8} There was no difference in survival proportions between HCQ users and CQ users.

In previous studies, the protective role of antimalarials was mainly concentrated on lupus nephritis.⁹ To further clarify this question, we performed univariate Cox proportional hazards regression analysis according to antimalarial exposure status on various clinical features. As shown in figure 1B, antimalarial drugs could exert their protective roles on a wide range of aspects, including but not limited to female gender, longer disease duration, a variety of organ involvement, hypocomplementemia and administration of glucocorticoids as well as cyclophosphamide. Besides renal involvement, patients with cardiopulmonary, gastrointestinal or haematological impairments also benefited from antimalarial treatment (all $p<0.0001$ by Kaplan-Meier survival analysis, figure 1C). Since antimalarials could

Table 1 Baseline characteristics of the patients with systemic lupus erythematosus by usage of antimalarials

	Antimalarial use		
Characteristic	User	Non-user	P values
Demographics			
Numbers of patients	562 (41.0%)	810 (59.0%)	
Women	526 (93.6%)	740 (91.4%)	ns
Age (years)	32.7 (12.1)	36.1 (12.6)	<0.0001
Disease characteristics			
Disease duration (years)*	3.1 (5.0)	3.7 (5.4)	ns
SLEDAI on admission	14.4 (7.4)	14.6 (8.8)	ns
SDI (≥1) on admission	1.4 (0.61)	1.6 (1.0)	ns
Organ involvements†			
Mucocutaneous	420 (74.7%)	494 (61.0%)	<0.0001
Neuropsychiatric	26 (4.6%)	66 (8.1%)	0.0113
Musculoskeletal	325 (57.8%)	419 (51.7%)	0.0276
Cardiopulmonary	91 (16.2%)	191 (23.6%)	0.0009
Gastrointestinal	114 (20.2%)	156 (19.3%)	ns
Ocular	5 (0.9%)	4 (0.5%)	ns
Renal	270 (48.0%)	431 (53.2%)	ns
Haematological	234 (41.6%)	383 (47.3%)	0.0412
Serology			
Anti-dsDNA positive	265 (50.4%)	376 (54.7%)	ns
Anti-Sm positive	164 (32.6%)	239 (34.3%)	ns
Anti-cardiolipin positive	69 (29.2%)	77 (29.7%)	ns
RF positive	112 (30.0%)	131 (27.7%)	ns
Low C3 complement‡	395 (76.6%)	489 (72.4%)	ns
Low C4 complement‡	343 (76.6%)	427 (76.8%)	ns
Medications			
Glucocorticoids	541 (96.3%)	723 (89.3%)	<0.0001
Cyclophosphamide	224 (40.0%)	358 (44.2%)	ns
Other immunosuppressants	104 (18.5%)	129 (15.9%)	ns
Comorbidities			
Hypertension	9 (1.6%)	22 (2.7%)	ns
Diabetes mellitus	26 (4.6%)	39 (4.8%)	ns
Infection	15 (2.7%)	22 (2.7%)	ns

*From the date of symptom onset to the date of first admission.

†Were assessed as Feng *et al*⁵ described.

‡Complement C3 <0.8 g/L, complement C4 <0.2 g/L.

ns, non-significant; RF, rheumatoid factor; SDI, Systemic Lupus International Collaborating and Clinics /American College of Rheumatology Damage Index ; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

Figure 1 (A) Survival curves of patients with systemic lupus erythematosus (SLE) divided by whether using antimalarial drugs. (B) Examinations of HRs of SLE patients' characters in using antimalarials. HRs are shown with 95% CI. (C) Comparisons of survival according to SLE patients' organ involvements and antimalarial usage. SDI, Systemic Lupus International Collaborating and Clinics /American College of Rheumatology Damage Index ; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

interference with the assembly of endosomal NADPH oxidase to inhibit the overactivity of immune system,¹ users were expected to have better outcomes than non-users when they were accompanied with vital organ involvements.

The effect of antimalarials on alleviating organ damage may also be related to lipid lowering,² glycaemic controlling³ and thrombosis prevention.⁴ In this cohort, 376 patients had the record of second hospitalisation before 2015, of which 165 received antimalarial treatment. Blood level of total cholesterol was lower in antimalarial treating group than the non-treated

group (4.47 ± 1.25 mmol/L vs 5.04 ± 2.17 mmol/L, $p < 0.05$), and there was no difference between the two groups in the first hospitalisation. Other metabolic data, such as systolic and diastolic blood pressure, fasting blood sugar, triglyceride and uric acid, were similar between the two groups in two times of hospitalisation. Although percentages of leucopenia, anaemia and thrombocytopenia were similar between antimalarial users and non-users during the first hospitalisation, non-users were more likely to be anaemia on their second inpatients visits (46.5% vs 58.2%, $p < 0.05$).

In conclusion, our data show that the use of antimalarials could improve long-term outcome of Chinese patients with SLE. These drugs possess protective effects on a wide range of clinical aspects. Patients with vital organ involvements, especially cardiopulmonary, gastrointestinal, renal or haematological impairments, may gain more benefits from antimalarial treatments.

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