Hydroxychloroquine dosing in systemic lupus erythematosus: response to 'Comment on the 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus by Fanouriakis *et al*' by Costedoat-Chalumeau *et al*

We thank Drs Costedoat-Chalumeau, Isenberg and Petri for their interest and insightful comments regarding hydroxychloroquine (HCQ) dosing in systemic lupus erythematosus (SLE).¹ The authors outline three major arguments against recommending a lower daily dose for HCQ: (1) the lower dose of 5 mg/kg real weight/day has not proven equal efficacy with the previous 6.5 mg/kg/day, (2) the patient population of the studies that suggest higher rates of HCQ-retinopathy (older patients, mostly with rheumatoid arthritis) does not correspond to the average patient with lupus and (3) established low adherence rates to HCQ reported in some studies, if combined with a lower prescribed dose, may potentially lead to HCQ undertreatment and blood levels below the presumed therapeutic range.

Indeed, whether the efficacy of the lower 5 mg/kg real body weight dose is equally efficacious compared with the older 6.5 mg/kg/day has not been tested in formal clinical studies, and this is already acknowledged in the manuscript.² Notably, the vast majority of evidence regarding the multiple beneficial effects of HCQ has not assessed different dosages (especially expressed in relation to body weight) or compliance to treatment; rather, they report on outcomes in association to whether the patients received the drug or not. Our recommendation was based on a single study in the USA,³ as well as a smaller study in an Asian population.⁴ Accordingly, this is reflected in the 3b/C level of evidence/grade of recommendation and, undoubtedly, more data are needed pertinent to the benefit/risk ratio of various HCQ dosages.

Yet, there is another side in this argument that weighted heavily in formulating these recommendations. SLE affects mostly young individuals and HCQ is strongly recommended as a *life-long* therapy, in the absence of contraindications. Consequently, SLE patients *by default* are expected to receive high cumulative doses of HCQ, only by their long disease duration, and thus, the risk for retinal toxicity is higher. Moreover, prescribing higher doses on the assumption of suboptimal patient compliance is arbitrary and not in line with treatment recommendations. Finally, basing dosing recommendations on HCQ blood concentration of a given patient (which reflects recent adherence)⁵ has not yet proven superiority in formal studies, nor is feasible in most centres treating patients with SLE.

In summary, while acknowledging the legitimate concerns of the authors about possible undertreatment, the field of HCQ-associated retinopathy is undergoing significant changes with the newer, more sensitive screening techniques for retinal toxicity, which are more likely to detect reversible retinopathy. Accordingly, screening should no more be performed only by funduscopy, which can detect retinopathy when it is too late. This is the

most important 'take-home' message of the updated European League Against Rheumatism recommendations for the management of SLE. The actual prescription dose will take into account individual patient and disease characteristics (age at diagnosis and clinical manifestations, among others), as well as physician practices, including the availability of HCQ level monitoring.

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