Response to: 'Hydroxychloroquine is neutral in risk of chronic kidney disease in patients with systemic lupus erythematosus' by Wu *et al*

We thank Drs Wu *et al* for their interest in our manuscript¹ and the stimulating data they provide regarding the value of hydroxychloroquine (HCQ) in the prevention of chronic kidney disease (CKD) in patients with systemic lupus erythematosus (SLE).² We agree with the authors that the evidence behind the recommendation for a 50% reduction in HCQ dose in patients with lupus nephritis (LN) and a glomerular filtration rate (GFR) less than 30% is not supported by high-level evidence (although it is known that excretion of the drug is carried out principally by direct renal clearance).^{3,4} Nevertheless, *CKD is considered a risk factor for the most important side effect of HCQ, retinal toxicity*; with newer, more sensitive screening techniques, the latter is now more frequently detected than in the past, reaching 10% to 20% after 20 or more years of use.^{5,6} Since HCQ is universally recommended as life-long therapy in SLE and the risk for ocular toxicity correlates with the cumulative dose (ie, daily dose and duration of intake), it was reasonable to recommend a lower dose for patients with severe CKD.

In their letter, the authors also provide data from the Taiwan National Health Insurance Research Database to question whether HCQ has an additive beneficial effect in preventing CKD in lupus patients. To this end, they analysed 783 newly diagnosed SLE patients who started HCQ treatment within 1 year from diagnosis and divided them into two groups according to their HCQ prescription coverage days for 1 year (less or more than 90 days, respectively). After propensity score matching, the authors found in their population no reduced risk of CKD in HCQ users for up to 14 years. We believe that the results of the authors' analysis should be interpreted with caution and certainly cannot be generalised—at this point—to other populations, without further confirmation. First, it is not clear what percentage of their patients had biopsy-proven LN (as opposed to only extrarenal SLE). Second, although the authors have reportedly adjusted for co-medications, it is unclear whether cumulative doses of drugs commonly used in LN, like glucocorticoids or cyclophosphamide, were comparable between the two groups. Lastly, regarding HCQ per se, the analysis has not taken into account the issue of patient adherence to treatment. Suboptimal adherence to HCQ in lupus patients has been consistently reported in several studies;^{7,8} thus, conclusions based on prescription data may not accurately predict actual taking of the drug.

Unlike extrarenal SLE, where the multiple benefits of HCQ have been established,⁹ data regarding the benefits of HCQ specifically in LN are less robust. As shown in our own systematic literature review informing the current recommendations for LN, most data originate from retrospective observational studies, wherein anti-malarials have been reported to reduce the risk for subsequent CKD, with OR ranging from 0.18 to 0.40.^{10–12} In view of current data, the European League Against Rheumatism/European Renal Association-European Dialysis and Transplant Association recommend the use of HCQ—unless contraindicated—in all patients with SLE and LN, with dose adjustments according to body weight and GFR.

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REFERENCES

- 1 Fanouriakis A, Kostopoulou M, Cheema K, *et al*. 2019 update of the joint European League against Rheumatism and European renal Association-European dialysis and transplant association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. *Ann Rheum Dis* 2020. doi:10.1136/annrheumdis-2020-216924. [Epub ahead of print: 27 Mar 2020].
- 2 C-Y W, Ye Z, Tan M, *et al*. Hydroxychloroquine is neutral in risk of chronic kidney disease in patients with systemic lupus erythematosus. *Ann Rheum Dis* 2020. doi:10.1136/annrheumdis-2020-217728
- 3 Furst DE. Pharmacokinetics of hydroxychloroquine and chloroquine during treatment of rheumatic diseases. *Lupus* 1996;5(Suppl 1):11–15.
- 4 Yokogawa N, Hashiguchi M, Nagai Y, *et al*. Pharmacokinetics of hydroxychloroquine in systemic lupus erythematosus patients with renal impairment [abstract]. *Arthritis Rheumatol* 2019;71.
- 5 Marmor MF, Kellner U, Lai TYY, *et al*. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). *Ophthalmology* 2016;123:1386–94.
- 6 Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. *JAMA Ophthalmol* 2014;132:1453–60.
- 7 Mok CC, Penn HJ, Chan KL, *et al*. Hydroxychloroquine serum concentrations and flares of systemic lupus erythematosus: a longitudinal cohort analysis. *Arthritis Care Res* 2016;68:1295–302.
- 8 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.
- 9 Fanouriakis A, Kostopoulou M, Alunno A, *et al*. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 2019;78:736–45.
- 10 Galindo-Izquierdo M, Rodriguez-Almaraz E, Pego-Reigosa JM, *et al*. Characterization of patients with lupus nephritis included in a large cohort from the Spanish Society of rheumatology registry of patients with systemic lupus erythematosus (RELESSER). *Medicine* 2016;95:e2891.
- 11 Pokroy-Shapira E, Gelernter I, Molad Y. Evolution of chronic kidney disease in patients with systemic lupus erythematosus over a long-period follow-up: a single-center inception cohort study. *Clin Rheumatol* 2014;33:649–57.
- 12 Okpechi IG, Ayodele OE, Jones ESW, *et al*. Outcome of patients with membranous lupus nephritis in Cape town South Africa. *Nephrol Dial Transplant* 2012;27:3509–15.