LUPUS SCIENCE & MEDICINE™

Dialogue: Hydroxychloroquine pharmacokinetic (PK) and exposure response in pregnancies with systemic lupus erythematosus: the importance of adherence for neonatal outcome

Bonnie Bermas ,[1] Nathalie Costedoat-Chalumeau[2,3]

To cite: Bermas B, Costedoat-Chalumeau N. Dialogue: Hydroxychloroquine pharmacokinetic (PK) and exposure response in pregnancies with systemic lupus erythematosus: the importance of adherence for neonatal outcome. *Lupus Science & Medicine* 2022;**9**:e000630. doi:10.1136/lupus-2021-000630

Received 22 December 2021
Accepted 23 December 2021

Linked

► http://dx.doi.org/10.1136/lupus-2021-000602

Check for updates

[1]Division of Rheumatic Diseases, UT Southwestern Medical, Dallas, Texas, USA
[2]Service de médecine interne, Centre de référence maladies autoimmunes et systémiques rares Île de France, APHP, Hopital Cochin, Paris, France
[3]Université de Paris, Centre de recherche épidémiologie et biostatistiques de Sorbonne Paris Cité, F-75004 Paris, France

Correspondence to
Dr Bonnie Bermas; Bonnie.Bermas@UTSouthwestern.edu

Hydroxychloroquine (HCQ) is the cornerstone of therapy for persons with SLE. Not only does it reduce morbidity and mortality, but also it improves maternal and fetal outcomes in pregnant women with SLE.[1] In spite of these benefits, claims data studies show that HCQ medication adherence during pregnancy is low.[2] Data suggest that measuring HCQ blood levels is an objective measure of non-adherence in patients with SLE.[3] However, during pregnancy, it is possible changes in drug pharmacokinetics (PK) may impact drug exposure.

In this issue of *Lupus Science and Medicine*, Balevic *et al* present data on significant changes in HCQ PK during pregnancy with a shortening of drug half-life by 10 days.[4] However, the authors noted that this change in PK had less of an effect on HCQ exposure during pregnancy than medication adherence. Overall, low HCQ levels resulted in higher rates of preterm birth.

The study evaluated serum levels of HCQ in 61 pregnancies in 56 women who were taking this medication a minimum of 3 months prior to pregnancy. Levels were defined as non-adherent ≤100 ng/mL to adherent >100 ng/mL. These levels were compared with patient-reported adherence using the Medication Adherence Self-Reported Inventory (MASRI). In this study, as shown by others, the MASRI score underestimated non-adherence. Neonatal outcomes were reported for 56 pregnancies and included two neonatal losses. In the 54 remaining pregnancies, two-thirds of the pregnancies with non-adherent HCQ concentrations delivered preterm, whereas 6.7% of those pregnancies with HCQ levels of 100 ng/mL–500 ng/mL delivered preterm. Paradoxically, 55.6% of pregnancies in which HCQ concentrations were >500 ng/mL delivered preterm as well.

This study adds nicely to the growing body of evidence that measurement of serum and blood levels of HCQ may more accurately correlate with adherence and be a better way of deciding drug dosing. It also supports what has been shown in other studies that HCQ can positively impact pregnancy outcome in patients with SLE.

There are several limitations to this study. Serum levels of HCQ are not as accurate as whole blood samples and not as well studied in pregnant patients with SLE. While the use of serum allowed for biorepository samples and may have helped with PK modelling, it does limit the applicability of the authors' findings. The authors attempted to correct for this by using a factor of approximately 2 to estimate whole blood concentrations.

Another shortcoming of this study is that the authors chose a cut-off of <100 ng/mL for non-adherence, a choice supported by the literature. However, they made the assumption that any dose >100 ng/mL was therapeutic. In Mok *et al*'s[5] study using whole blood samples, ranges between 100 ng/mL and 500 ng/mL were considered subtherapeutic, whereas ranges >500 ng/mL were considered therapeutic. Even allowing for the serum correction factor above, this leaves several patients in the adherent group likely to be subtherapeutic.

An important finding reported here is that patients with HCQ levels of <100 ng/mL delivered preterm. While the authors did sensitivity analysis that controlled for azathioprine and prednisone use—two medications associated with preterm birth—it is possible that patients who were non-adherent to HCQ may have

been non-adherent to other medications as well, and this too could have impacted pregnancy outcome. The role of repeated vomiting (including on the intake of low-dose aspirin if prescribed) could also explain both findings (low HCQ concentrations and poor outcome). Moreover, the CIs of this finding were wide, lessening its impact. The authors' paradoxical finding of increased preterm birth in those with HCQ concentrations >500 ng/mL warrants further explanation and study. While arguably patients with the worst renal disease may have decreased HCQ clearance that resulted in higher HCQ concentrations, one cannot assume this is the case. In Mok *et al*'s study,[5] HCQ levels were not associated with renal disease or renal function as estimated by glomerular filtration rate. Future studies of HCQ levels during pregnancy may provide larger numbers of subjects to better elucidate other factors that impact drug levels.

HCQ adherence in patients with SLE remains problematic. This is particularly so in pregnant women, in spite of evidence that HCQ improves pregnancy outcomes for both the mother and the fetus. How to best assess HCQ adherence is also up for debate. Nonetheless, recent data suggest that measuring whole blood levels (or as in the case of this paper serum levels) will likely yield a more accurate picture of adherence and PK alterations during pregnancy. The resulting impact on choice of HCQ dosing will likely translate into improved disease activity in our patients with lupus whether pregnant or not.

Contributors Both NC-C and BB contributed equally to this piece.

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 and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study does not involve human participants.

Provenance and peer review Commissioned; internally peer reviewed.

ORCID iD

Bonnie Bermas http://orcid.org/0000-0002-1007-4084

REFERENCES

1 Janardana R, Haridas V, Priya V, *et al*. Maternal and fetal outcomes of lupus pregnancies: a collective effort by Karnataka rheumatologists. *Lupus* 2020;29:1397–403.
2 Bermas BL, Kim SC, Huybrechts K, *et al*. Trends in use of hydroxychloroquine during pregnancy in systemic lupus erythematosus patients from 2001 to 2015. *Lupus* 2018;27:1012–7.
3 Costedoat-Chalumeau N, Pouchot J, Guettrot-Imbert G, *et al*. Adherence to treatment in systemic lupus erythematosus patients. *Best Pract Res Clin Rheumatol* 2013;27:329–40.
4 Balevic SJ, Weiner D, Clowse MEB. Hydroxychloroquine pK and exposure-response in pregnancies with lupus: the importance of adherence for neonatal outcomes. *Lupus Sci Med* 2021.
5 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.