chloroquine, desethylchloroquine and bidesethylchloroquine. From chloroquine, which differs from HCQ by just 1 hydroxyl group, it can be extrapolated that HCQ is possibly metabolized by the same cytochromes (CYPs) as those for chloroquine, that is, CYP2C8 and CYP3A and to a lesser extent by CYP2D6.[4,5] CYP2D6 polymorphism has been demonstrated to correlate with variations in HCQ metabolism among Korean lupus patients.[4] Another study also found metabolism of amodiaquine, which is structurally related to HCQ, to be impaired in patients with CYP2C8 polymorphisms.[6] Concurrent administration of drugs that are metabolized through CYP2C8, CYP3A4, and CYP2D6 (eg, metoprolol, fluoxetine, and venlafaxine) will compete with HCQ for metabolism and lead to increased levels of HCQ.[2]

The medical community is generally not aware of the pharmacokinetics of HCQ, as it is not well detailed in standard drug references. Clinicians should be aware of the variability of HCQ pharmacokinetics and understand that dose is just one of the many factors affecting drug exposure. Toward the end of their paper, the authors put forward the question of whether therapeutic drug monitoring could solve the dosage controversy by providing more direct guidance to prescribers. We agree that drug level, rather than drug dosage per se, better informs clinicians about actual HCQ exposure. Measuring drug level removes the uncertainty of drug exposure associated with the highly variable pharmacokinetics and drug interactions. However, therapeutic drug monitoring is reactive in nature. Precision of initial dosages could be optimized by taking into account factors such as genotyping (eg, the metabolizer status of CYP2C8). Future studies should explore the cutoff values of efficacy and toxicity for HCQ serum level and aim at providing evidence of benefit and safety with HCQ therapeutic drug monitoring. Researchers should also investigate incorporating genotyping in the dosage algorithm of HCQ as part of the effort to achieve personalized medicine.

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Reply to Comment on: Rethinking the Hydroxychloroquine Dosing and Retinopathy Screening Guidelines

EDITOR:

WE APPRECIATE THE COMMENTS FROM LAW AND ASSOCIates regarding our Perspective. They reiterate that pharmacokinetics (PK) of hydroxychloroquine (HCQ) are variable and that a daily dose produces variable blood concentrations depending on genetic factors, absorption variables, and effects of induction and inhibition of metabolizing enzymes, all topics that we reviewed in a previous publication.[1]

Both pharmacokinetics and the pharmacodynamics studies are helpful to determine the therapeutic dose. When HCQ was first approved in 1955, neither placebo-controlled trials nor formal PK/pharmacodynamic studies were performed. However, the current conventional dosage has evolved over decades of clinical use and largely demonstrates efficacy and long-term safety.[2,3] Recently, HCQ therapy, used at much higher-than-conventional dosages, has been tried for several nonrheumatic conditions. Two of 7 patients (28.6%) receiving 1,000 mg/day for non–small cell lung cancer[4] and 3 of 12 patients (25%) receiving 800 mg/day for chronic graft versus host disease[5] experienced early onset HCQ retinopathy. Meanwhile, in patients receiving 200-400 mg/day with a ceiling daily dose of 6.5 mg/kg, for the ideal body weight for patients with systemic lupus erythematosus, early onset HCQ retinopathy is rare, although it occurred in a patient with high blood level of HCQ.[6]

Law and associates recommend monitoring of therapeutic drug levels of HCQ. We agree that this will be more objective than monitoring daily prescribed dosages. However, there are few data relating drug levels, duration of exposure, and onset and progression of HCQ retinopathy. Until we have replicated research showing the relationship of drug level and retinopathy, some form of weight-based dosages will be prevalent in clinical practice, and guidelines will need to be refined as suggested in the Perspective.

Law and associates also characterized therapeutic drug monitoring as reactive, compared to precision dosing using genotype and metabolizer status. Respectfully, we disagree. To our knowledge, no publication has attempted to predict a drug level based on pretreatment genotyping and typing the metabolizing enzymes of a patient. All the correlations published are retrospective and insufficiently tight to permit guidance in dosing.[7] Clinically, drug level testing is practical and widespread and is used with other drugs such as amikacin, amiodarone, digoxin, and many others. Drug level testing already allows rheumatologists to uncover poor adherence with prescribed HCQ therapy. If drug level testing proves to correlate HCQ retinopathy reproducibly and without wide variance, it will be embraced by ophthalmologists as well.

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