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Reply

To the Editor:

We thank Dr. Riddle for stating his concerns regarding potential methodologic issues in our study. We would like to address these concerns.

First, our article was prepared in compliance with the Consolidated Standards of Reporting Trials statement (1), including all prespecified methods and results; therefore, there is no concern of selective outcome reporting. Diclofenac etalhyaluronate (DF-HA) is a developmental product and has never been on the market in any country. To protect our intellectual property, only the minimum information was provided to the registry. Therefore, some of the secondary outcomes reported in this article differ from those registered. However, the registered contents in the JapicCTI registry follow the International Federation of Pharmaceutical Manufacturers and Associations guidelines (2). We plan to add this article to the JapicCTI registry after DF-HA becomes available in the first country to implement it.

As for the second concern, we used the WOMAC scoring system (3) correctly because we followed the instructions in the WOMAC user guide to normalize dimensions on a subscale-by-scale basis and express the scores on 0–10 or 0–100 scales (4). Dr. Riddle also raised the issue of incorrect reporting of scale version and type of scale, as described by Woolacott et al (5). In the outcomes section of our article, however, we clearly state that we used a 100-mm VAS to evaluate the WOMAC pain subscale scores. Therefore, we do not inadequately report or misreport any application or explanations of the WOMAC pain subscale scoring system.

Third, it is necessary to examine multiple factors in order to evaluate the clinical importance of group differences (6). We discussed results of the responder analysis, improvement of multiple symptoms, early response to treatment with DF-HA, and maintenance of the treatment effect. In addition, to examine the magnitude of group differences for the primary and secondary outcomes, the mean effect size over 12 weeks was calculated using the least squares mean change and the pooled SD at each time point for the post hoc analyses (7). The results indicated that the mean effect size of DF-HA treatment on WOMAC pain subscale scores over 12 weeks was 0.30. Similar effect sizes were observed when secondary outcomes were evaluated in the DF-HA group over 12 weeks (Table 1). Although this study was not an active treatment–controlled clinical trial, and it is difficult to evaluate the clinical importance of group differences only by effect size, the effect size of DF-HA was in the low-to-moderate range for improvement in primary and secondary outcomes (8). Thus, some benefits of DF-HA were confirmed, but further studies are needed to evaluate the clinical usefulness of DF-HA.

Table 1. Difference and effect size in primary and secondary outcomes of DF-HA over 12 weeks*

	Difference (95% CI)	Effect size, SD units
Primary outcome		
WOMAC pain score, mm†	−6.1 (−9.4, −2.8)	0.30
Secondary outcomes		
WOMAC stiffness score, mm†	−4.6 (−8.0, −1.2)	0.20
WOMAC physical function score, mm†	−5.7 (−8.9, −2.5)	0.29
Total score	−5.6 (−8.7, −2.4)	0.29
50-foot walking test pain score, mm†	−6.8 (−10.5, −3.2)	0.30
Mean daily pain score‡	−0.56 (−0.82, −0.31)	0.35
Patient global assessment score, mm†	−6.5 (−9.7, −3.3)	0.31
Physician global assessment score, mm†	−4.5 (−7.2, −1.9)	0.24

* Differences are the between-group difference (95% confidence interval [95% CI]) in least squares mean change from baseline. DF-HA = diclofenac etalhyaluronate; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
† On a 100-mm visual analog scale (0–100).
‡ On an 11-point numeric rating scale (0–10).

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Yoshihiro Nishida, MD
Nagoya University Hospital
Nagoya, Japan
Kazuyuki Kano, BSc
Yuji Nobuoka, MSc
Takayuki Seo, PhD
Seikagaku Corporation
Tokyo, Japan

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More steps forward to optimize the dosing of hydroxychloroquine: comment on the article by Petri et al

To the Editor:

We read with great interest the article by Dr. Petri and colleagues describing their study in which it was demonstrated that higher hydroxychloroquine (HCQ) blood levels were associated with lower risk of thrombotic events in patients with systemic lupus erythematosus (SLE) (1). A threshold of ≥1,068 ng/ml for whole blood HCQ levels (based on tertiles of mean levels observed in SLE patients) and a most recent HCQ level of ≥1,192 ng/ml had a protective effect. The dose response observed in that study implies that HCQ has a therapeutic threshold with which to determine protective versus deleterious effects. However, a previous study indicated that an HCQ blood level ranging from 1,177 ng/ml to 3,513 ng/ml was predictive of HCQ retinopathy (2). Obviously, there is a great overlap between HCQ blood levels that are protective against thrombosis and toxic levels associated with retinopathy. The optimal therapeutic range is so narrow (1,068–1,177 ng/ml) that dose titration to target this level would be difficult in clinical practice. It seems that the dilemma of avoiding retinopathy while maintaining the benefit of HCQ still exists.

To further clarify this problem, we believe more comprehensive risk stratification is helpful. As "triple positivity" for antiphospholipid antibodies carries higher risk of thrombotic events (3), the presence of anti–β_2-glycoprotein I and anticardiolipin antibodies would have been important to identify, but was not reported in the analysis by Petri and colleagues. The concomitant use of aspirin may modify the risk of thrombosis, which was also not specified in the report. In addition, Petri and colleagues demonstrated that the risk of thrombosis was reduced by 13% with every 200-ng/ml increase in HCQ blood level. We are curious if this observation still holds true for higher HCQ blood levels (e.g., >1,500 or >2,000 ng/ml). Similarly, the risk of retinopathy should be assessed in stratified groups of patients displaying higher ranges of HCQ blood levels, in order to clarify the extent of hazard conferred by each HCQ blood level range among patients who require this therapy. This would help physicians and patients manage the disease in a way that balances the risks and benefits of treatment with HCQ.

Finally, the strategy of adapting HCQ dose based on blood level with an aim at reducing thrombotic risk should be investigated in the future. A similar approach was shown to be ineffective in decreasing disease flares of SLE in the PLUS study (4). Although personalized drug dosing and risk management will likely be the future paradigm in the treatment of SLE, we still need more details on the relationship between the dose of HCQ and the benefit or toxicity associated with this treatment.

Jui-Hung Kao, MD
Ting-Yuan Lan, MD
Ko-Jen Li, MD, PhD
National Taiwan University Hospital
Taipei, Taiwan

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Reply

To the Editor:

We would like to thank Dr. Kao and colleagues for their comments regarding our article, and we have some thoughts in response.