

## Chronic hydroxychloroquine exposure and the risk of Alzheimer's disease

Hydroxychloroquine is an immunomodulatory agent which is commonly used to treat malaria and autoimmune diseases.<sup>1</sup> The association between hydroxychloroquine therapy and subsequent comorbidities has been extensively addressed.<sup>1,2</sup> Recently, a cohort study conducted in the UK by Fardet *et al* published in *Annals of the Rheumatic Diseases* reported that long-term use of hydroxychloroquine was not associated with the risk of Alzheimer's disease when compared with non-use of hydroxychloroquine (adjusted HR=0.81, 95% CI=0.58 to 1.12, p=0.20).<sup>3</sup> One comment published in *Annals of the Rheumatic Diseases* reported that due to conflicting results between observational studies regarding the impact of hydroxychloroquine on Alzheimer's disease, the relationship cannot be determined currently.<sup>4</sup>

In order to test such an association in a different population, a preliminary case-control study was conducted using the 2005–2012 database of the Taiwan National Health Insurance Program with 23 million people living in Taiwan.<sup>5</sup> People aged ≥65 years with newly diagnosis of Alzheimer's disease were assigned as the cases (according to International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-9 code 331.0). People aged ≥65 years without any type of dementia were selected as the controls. In order to reduce the biased results, people who had a cumulative period of hydroxychloroquine use <3 months were excluded from the study. Table 1 revealed that there was no statistical association between Alzheimer's disease and hydroxychloroquine use (crude OR=0.97, 95% CI=0.50 to 1.87, p=0.92), which was compatible with Fardet *et al*'s cohort study reporting no statistical association between hydroxychloroquine use and the risk of Alzheimer's disease. Due to only nine cases with Alzheimer's disease ever using hydroxychloroquine in our study, further research with a large case number is required to confirm our finding. Among quinoline-based antimalarial drugs, hydroxychloroquine does not have a good ability to penetrate the blood–brain barrier.<sup>6</sup> It is not a rational hypothesis that hydroxychloroquine use can have an impact on the risk of Alzheimer's disease clinically. Those studies showing an association between hydroxychloroquine use and the risk of Alzheimer's disease should be interpreted with caution. We agree with the author's comments that there is no conclusive evidence linking hydroxychloroquine use and the risk of Alzheimer's disease,<sup>4</sup> regardless of the population studied. Randomised controlled trials are needed to explore the issue. In view of the above discussion, older people who are on long-time therapy of hydroxychloroquine do not need to worry about the risk of Alzheimer's disease because such a risk has not

**Table 1** Association between Alzheimer's disease and hydroxychloroquine therapy in people aged ≥65 years in 2005–2012

	Alzheimer's disease (n=1131)	Non-dementia (n=92 063)	Crude OR (95% CI)	P value
Hydroxychloroquine use	9 (0.80)	758 (0.82)	0.97 (0.50 to 1.87)	0.920
No use	1122 (99.20)	91 305 (99.18)	1	

yet been confirmed. Finally, Fardet *et al*'s research has impressed the readers a lot and has drawn much attention from scholars specialising in this issue.

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Handling editor Josef S Smolen

**Contributors** S-WL contributed to the conception of the article, initiated the draft of the article and has approved the final draft submitted. Y-HK and K-FL conducted data analysis.

**Funding** This study was funded by the MOST Clinical Trial Consortium for Stroke, grant number: MOST 108-2321-B-039-003; the Ministry of Health and Welfare in Taiwan, grant number: MOHW108-TDU-B-212-133004; the Academia Sinica Stroke Biosignature Project, grant number: BM10701010021; and the China Medical University Hospital in Taiwan, grant number: DMR-107-192 and DMR-108-089. These funding agencies did not influence the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** Insurance reimbursement claims data used in this study were available for public access. Patient identification numbers had been scrambled to ensure confidentiality. Patient informed consent was not required. This study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115).

**Provenance and peer review** Not commissioned; internally peer reviewed.

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**To cite** Lai S-W, Kuo Y-H, Liao K-F. *Ann Rheum Dis* 2021;**80**:e105.

Received 14 August 2019

Accepted 16 August 2019

Published Online First 21 August 2019



► <http://dx.doi.org/10.1136/annrheumdis-2019-216182>

*Ann Rheum Dis* 2021;**80**:e105. doi:10.1136/annrheumdis-2019-216173

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