Chronic hydroxychloroquine/chloroquine exposure for connective tissue diseases and risk of Alzheimer's disease

I have read with interest the article by Fardet *et al*¹ regarding chronic hydroxychloroquine/chloroquine exposure for connective tissue diseases and risk of Alzheimer's disease. This population-based cohort study reported that people who had been chronically exposed to hydroxychloroquine/chloroquine were not at a higher risk of Alzheimer's disease than the control individuals. However, the manuscript has some issues. The results reported by Fardet *et al* differ from those of another retrospective case-control study² which demonstrated that patients with rheumatoid arthritis who used conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) including hydroxychloroquine showed a significant association with dementia. First, the risk of confounding may be significant in observational studies, and statistical adjustment for confounders in observational studies may not entirely resolve these problems. Second, the results from observational studies might be spurious due to some types of bias, such as reporting and recall biases. Considering the lack of evidence from randomised controlled trials (RCTs), the conclusions by Fardet *et al*¹ that hydroxychloroquine/chloroquine do not confer protection against the development of Alzheimer's disease and those by Chou *et al*² that csDMARD use increases the risk of Alzheimer's disease may be overstated or risky.³ The antimalarial drugs, hydroxychloroquine and chloroquine, have well-documented, anti-inflammatory activity and effectively suppress microglial neurotoxicity induced by β -amyloid protein.⁴ Currently, no RCTs have examined the role of hydroxychloroquine/chloroquine in preventing Alzheimer's disease. Whether hydroxychloroquine/chloroquine increases or decreases the development of Alzheimer's disease cannot yet be confidently stated. With respect to the divergent results from observational studies, well-designed RCTs are required to adequately address the complex problem about the relationship between hydroxychloroquine/chloroquine use and Alzheimer's disease risk.

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