What is the role of hydroxychloroquine in reducing thrombotic risk in patients with antiphospholipid antibodies?

Tzu-Fei Wang[1] *and Wendy Lim*[2]

[1]*Division of Hematology, Department of Medicine, The Ohio State University, Columbus, OH; and*
[2]*Department of Medicine, McMaster University, Hamilton, ON, Canada*

A 35-year-old man presents with an acute unprovoked deep vein thrombosis of the left lower extremity. He is treated with anticoagulation and elects to discontinue treatment after 6 months. He subsequently develops polyarthralgias, fatigue, and a malar rash, and a diagnosis of systemic lupus erythematosus is made based on laboratory and clinical findings. Additional laboratory testing reveals persistent triple positive antiphospholipid antibodies, including lupus anticoagulant, high titer anticardiolipin antibodies, and anti–β_2-glycoprotein I antibodies. The patient is reinitiated on anticoagulation, and the patient's rheumatologist inquires if the addition of hydroxychloroquine could help to prevent recurrent thrombosis.

Learning Objective

- Review the evidence supporting the use of hydroxychloroquine for primary and secondary prevention of thrombosis in patients with persistently positive antiphospholipid antibodies

Discussion

Antiphospholipid syndrome (APS) is diagnosed when a patient fulfills both the laboratory and clinical international classification criteria for APS.[1] Patients meet the laboratory criteria if they have ≥2 positive tests for an antiphospholipid antibody (aPL; including lupus anticoagulant, anticardiolipin antibody, and/or anti–β_2-glycoprotein I antibody) measured ≥12 weeks apart. Clinical criteria include either arterial or venous thrombosis or pregnancy morbidity.[1] Patients with APS have a high risk of recurrent thrombosis, and the current standard of care for these patients is long-term anticoagulation.[2] However, despite adequate anticoagulation, up to 5% to 10% of patients with APS may have recurrent thrombosis.[2,3] Additionally, the optimal management of patients with persistently positive aPL and no history of thrombosis remains unclear.[4] This problem is especially relevant in patients with systemic lupus erythematosus (SLE), where ≥1 aPLs are identified in 11% to 86% of patients with SLE[5] and may be associated with an increased risk of thrombosis.[6,7] Preventing recurrent thrombosis in a patient with APS (secondary prevention) and preventing a first-episode thrombosis in a patient with aPL (primary prevention) using a nonanticoagulant agent that reduces thrombotic risk without increasing bleeding risk is therefore of great interest.

One such agent is hydroxychloroquine (HCQ), an antimalarial drug with anti-inflammatory and immunomodulatory properties. It is one of the first-line agents in the treatment of SLE. HCQ is effective in reducing joint pain and inflammation in these patients and is well tolerated with few side effects.[8] Previous studies have demonstrated that HCQ blocks platelet aggregation and adhesion, improves cholesterol profiles,[9] and lowers the odds of having a persistently positive aPL.[10] Early reports suggested a protective effect of HCQ in reducing thromboembolic complications in patients with SLE.[11] Subsequent studies have evaluated HCQ for primary and secondary prevention of thrombosis in patients with aPL, with or without SLE.

To evaluate the evidence supporting HCQ for the prevention of thrombosis in patients with aPL, we conducted a PubMed search using the terms "Hydroxychloroquine" and "Thrombosis" and "Antiphospholipid Antibodies" or "Antiphospholipid Syndrome" or "aPL" (search completed June 18, 2016). Our primary outcome was the incidence of thrombosis in aPL-positive patients treated with HCQ compared with the incidence in non–HCQ-treated aPL-positive patients. We excluded non–English language studies and studies with pregnancy morbidity as the only reported outcome. Our search yielded 77 unique articles, of which 66 were excluded after title and abstract review (5 non-English, 9 pregnancy-related outcomes, 6 nonhuman studies, 13 without reported thrombotic outcomes, and 33 reviews without original data). Of the remaining 11 articles, 5 were excluded after reviewing the manuscripts (3 reviews, 1 did not report thrombotic outcomes, and 1 did not provide data on HCQ use). The references cited in the review articles revealed an additional 5 manuscripts. Therefore, a total of 11 studies were included in this review: 4 prospective studies,[12-15] 6 retrospective studies,[6,7,16-19] and 1 patient-level meta-analysis.[20] There were no randomized controlled trials. All studies combined arterial and venous thrombosis as the thrombosis outcome of interest.

Table 1 summarizes the 11 included studies. The majority (n = 9) of the studies assessed HCQ for primary prevention of thrombosis in patients with SLE. Almost all studies reported the hazard ratio (HR) or odds ratio (OR) of thromboembolism in patients on HCQ (at any time) compared with patients who never used HCQ, with 4 studies reporting these data stratified by aPL status (positive compared with negative aPL).[6,16,17,20] Among the 9 studies in patients with SLE, 5 showed a significant reduction in thrombosis in patients who used HCQ at any time during the study period (Table 1). The reported OR or HR in these studies ranged from 0.21 to 0.99. Among the 4 studies that did not achieve statistical significance, the point estimates all suggested a trend toward reduction of thrombosis among HCQ

Conflict-of-interest disclosures: The authors declare no competing financial interests.

Off-label drug use: hydroxychloroquine for the use of thrombosis prevention.

Table 1. Summary of studies investigating HCQ use in patients with aPL, with and without SLE

Author/year	Study design	N	aPL measurements (positive rate)	% of HCQ or use of antimalarials	Intervention/ comparison	Results (thrombosis rate)
SLE, primary prevention						
Wallace et al 1993[16]	Retrospective cohort	96	NA (100% positive)	NA	HCQ ever use vs no use	11% in HCQ users vs 20% in nonusers
Ho et al 2005[12]	Prospective cohort	442	≥1 (positivity rate NA)	NA	HCQ ever use vs no use	OR 0.54 (95% CI, 0.30-0.95) (univariate)*
Mok CC et al 2005[13]	Prospective cohort	625	≥1 (38.4% positive)	NA	HCQ ever use vs no use	OR 0.73 (95% CI, 0.38-1.40)*,†
Mok MY et al 2005[17]	Retrospective cohort	83	≥2, ≥6 weeks apart (100% positive)	55.9%	HCQ ever use vs no use	HR 0.21 (95% CI, 0.06-0.81)
Ruiz-Irastorza et al 2006[14]	Prospective cohort	232	≥1 (45.6% positive)	64%	Antimalarials‡ ever use vs no use	HR 0.28 (95% CI, 0.08-0.90)*
Tektonidou et al 2009[6]	Retrospective case-control	144	≥2, ≥12 weeks apart (100% positive)	70%	HCQ ever use vs no use	HR per month of use: 0.99 (95% CI, 0.98-1.00)
Kaiser et al 2009[7]	Retrospective cohort	1930	≥1 (27% positive)	80%	HCQ ever use vs no use	HR 0.67 (95% CI, 0.50-0.90)*
Jung et al 2010[18]	Retrospective, nested case-control	162	≥1 (27.4% positive)	32.7%	Antimalarials‡ ever use vs no use‡	OR 0.32 (95% CI, 0.14-0.74) (multivariate)*
Arnaud et al 2015[20]	Patient level meta-analysis	192	NA (100% positive)	43.8%	HCQ ever use vs no use	HR: 0.67 (95% CI, 0.34-1.32)§
aPL, positive primary prevention						
Erkan et al 2002[19]	Retrospective, cross-sectional	133	≥2, ≥6 weeks apart (100% positive)	Use of HCQ: 4/77 (5.2%) APS patients vs aPL-positive patients ($P < 0.001$)		21/56 (37.5%) asymptomatic
APS, secondary prevention						
Schmidt-Tanguy et al 2013[15]	Prospective nonrandomized	40	≥2, ≥12 weeks apart	50%	HCQ plus OA vs OA only	0% in HCQ users vs 30% in nonusers ($P = .0086$)

NA, not available/unknown; OA, oral anticoagulation.
*OR/HR was calculated by including all study patients, only some of whom were aPL positive. OR/HR not marked by an asterisk were based on only patients with positive aPL.
†For venous thrombosis only. The arterial thrombosis rate was reported to be similar (data not shown).
‡Antimalarials include HCQ or chloroquine or both.
§The study included a total of 497 patients, but the only available HR for HCQ use was calculated from the 192 patients with SLE.

users.[12,13,16,20] In a retrospective cohort of patients with SLE and aPL, 11% of patients who had been on HCQ at any time during the study developed thrombosis, compared with 20% of those who never took HCQ.[16] Although this risk reduction was not statistically significant, most patients (72%) in the HCQ group who developed thrombosis had events prior to starting HCQ. For the 4 studies stratified by aPL status,[6,16,17,20] only results pertaining to patients with positive aPL in these studies are summarized in Table 1. Two studies demonstrated a significant reduction of the risk of thrombosis in HCQ users.[6,17] Although the other 2 did not meet statistical significance, they again showed a trend toward a risk reduction.[16,20] Based on these data, the 14th International Congress on APS Treatment Task Force has recommended HCQ use in all patients with SLE and positive aPL testing.[21] Our review of the evidence supports this recommendation as grade 2B, based on the lack of randomized controlled trials.

Of the 2 remaining studies included in our review, one was a primary prevention study in aPL-positive patients (without a history of thrombosis)[19] and the other was a secondary prevention study in patients with APS.[15] The first study was a retrospective cross-sectional study comparing HCQ use in patients with APS (positive aPL with thrombosis) to aPL-positive patients without thrombosis. The study revealed that the use of aspirin and/or HCQ was associated with a decreased risk of thrombosis in aPL-positive patients based on logistic regression analysis.[19] However, this study was limited by a small sample size, retrospective design, unbalanced patient characteristics in each group, and the combined analysis of aspirin with HCQ, so the results should be interpreted with caution. The second study was a prospective nonrandomized trial investigating the role of HCQ for secondary prevention of thrombosis in patients with primary APS (note that none of these patients had underlying SLE). Forty patients were enrolled into 2 groups: standard oral anticoagulation or oral anticoagulation plus HCQ 400 mg daily.[15] After 3 years of treatment, the incidence of recurrent thrombosis was markedly different: 30% in patients treated with standard anticoagulation compared with 0% in patients treated with a combination of anticoagulation and HCQ (HR, 2.4; 95% confidence interval [CI], 1.3-4.1; $P < .005$). The 2 groups did not differ significantly in other risk factors for thrombosis. This remains the only prospective study using HCQ as an adjunct to anticoagulation for secondary prevention of VTE in patients with APS. Although intriguing, these results should be confirmed in future prospective trials.

The role of HCQ for the primary prevention of thrombosis in patients with positive aPL in the absence of SLE remains unclear. As well, the role of HCQ for the secondary prevention of thrombosis in patients with SLE is also unclear, as many patients with SLE already receive HCQ, and there are no clinical studies specifically addressing thrombotic rates in patients with SLE receiving, and not receiving, HCQ. A clinical trial examining HCQ use for primary prevention of thrombosis in aPL-positive patients without autoimmune disease (#NCT01784523) was terminated prematurely in 2015 due to a low recruitment rate, a

manufacturing shortage, and a price increase in HCQ. It is unlikely that such a large-scale study will be undertaken again in the near future.

Summary

In patients with SLE and persistently positive aPL, we recommend HCQ for the primary prevention of thrombosis (grade 2B). In patients without SLE but persistently positive aPL, we recommend against the routine use of HCQ as primary prevention of thrombosis, given the lack of evidence (grade 2C). Although there is no direct evidence supporting HCQ for the secondary prevention of thrombosis in patients with SLE and APS, HCQ is often used as part of the standard treatment regimen for SLE. Although HCQ may reduce thrombotic risk in these patients, in the absence of specific studies, we have not provided a recommendation for this group of patients. In patients without SLE but with APS, we recommend against the routine use of HCQ as secondary prevention of thrombosis (grade 2C). However, consideration may be given on a case-by-case basis, given the low toxicity of HCQ and potential benefits.[21]

For the patient illustrated in the clinical vignette, the diagnosis of SLE and the well-tolerated nature of HCQ support initiation of HCQ, in conjunction with anticoagulation for the management of APS.

Correspondence

Tzu-Fei Wang, Division of Hematology, Department of Medicine, The Ohio State University, 320 W 10th Ave, A340, Columbus, OH 43210; e-mail: Tzu-Fei.Wang@osumc.edu.

References

1. Miyakis S. International consensus statement on an update of the preliminary classification criteria for antiphospholipid syndrome. *J Thromb Haemost*. 2006;4:295-306.
2. Crowther MA, Ginsberg JS, Julian J, et al. A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. *N Engl J Med*. 2003;349(12):1133-1138.
3. Finazzi G, Marchioli R, Brancaccio V, et al. A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). *J Thromb Haemost*. 2005;3(5):848-853.
4. Metjian A, Lim W. ASH evidence-based guidelines: should asymptomatic patients with antiphospholipid antibodies receive primary prophylaxis to prevent thrombosis? *Hematology Am Soc Hematol Educ Program*. 2009;2009:247-249.
5. Petri M. Epidemiology of the antiphospholipid antibody syndrome. *J Autoimmun*. 2000;15(2):145-151.
6. Tektonidou MG, Laskari K, Panagiotakos DB, Moutsopoulos HM. Risk factors for thrombosis and primary thrombosis prevention in patients with systemic lupus erythematosus with or without antiphospholipid antibodies. *Arthritis Rheum*. 2009;61(1):29-36.
7. Kaiser R, Cleveland CM, Criswell LA. Risk and protective factors for thrombosis in systemic lupus erythematosus: results from a large, multiethnic cohort. *Ann Rheum Dis*. 2009;68(2):238-241.
8. Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. *Ann Rheum Dis*. 2010;69(1):20-28.
9. Al-Homood IA. Thrombosis in systemic lupus erythematosus: a review article. *ISRN Rheumatol*. 2012;2012:428269.
10. Broder A, Putterman C. Hydroxychloroquine use is associated with lower odds of persistently positive antiphospholipid antibodies and/or lupus anticoagulant in systemic lupus erythematosus. *J Rheumatol*. 2013;40(1):30-33.
11. Wallace DJ. Does hydroxychloroquine sulfate prevent clot formation in systemic lupus erythematosus? *Arthritis Rheum*. 1987;30(12):1435-1436.
12. Ho KT, Ahn CW, Alarcón GS, et al. Systemic lupus erythematosus in a multiethnic cohort (LUMINA): XXVIII. Factors predictive of thrombotic events. *Rheumatology (Oxford)*. 2005;44(10):1303-1307.
13. Mok CC, Tang SS, To CH, Petri M. Incidence and risk factors of thromboembolism in systemic lupus erythematosus: a comparison of three ethnic groups. *Arthritis Rheum*. 2005;52(9):2774-2782.
14. Ruiz-Irastorza G, Egurbide MV, Pijoan JI, et al. Effect of antimalarials on thrombosis and survival in patients with systemic lupus erythematosus. *Lupus*. 2006;15(9):577-583.
15. Schmidt-Tanguy A, Voswinkel J, Henrion D, et al. Antithrombotic effects of hydroxychloroquine in primary antiphospholipid syndrome patients. *J Thromb Haemost*. 2013;11(10):1927-1929.
16. Wallace DJ, Linker-Israeli M, Metzger AL, Stecher VJ. The relevance of antimalarial therapy with regard to thrombosis, hypercholesterolemia and cytokines in SLE. *Lupus*. 1993;2(Suppl 1):S13-S15.
17. Mok MY, Chan EY, Fong DY, Leung KF, Wong WS, Lau CS. Antiphospholipid antibody profiles and their clinical associations in Chinese patients with systemic lupus erythematosus. *J Rheumatol*. 2005;32(4):622-628.
18. Jung H, Bobba R, Su J, et al. The protective effect of antimalarial drugs on thrombovascular events in systemic lupus erythematosus. *Arthritis Rheum*. 2010;62(3):863-868.
19. Erkan D, Yazici Y, Peterson MG, Sammaritano L, Lockshin MD. A cross-sectional study of clinical thrombotic risk factors and preventive treatments in antiphospholipid syndrome. *Rheumatology (Oxford)*. 2002;41(8):924-929.
20. Arnaud L, Mathian A, Devilliers H, et al. Patient-level analysis of five international cohorts further confirms the efficacy of aspirin for the primary prevention of thrombosis in patients with antiphospholipid antibodies. *Autoimmun Rev*. 2015;14(3):192-200.
21. Erkan D, Aguiar CL, Andrade D, et al. 14th International Congress on Antiphospholipid Antibodies: task force report on antiphospholipid syndrome treatment trends. *Autoimmun Rev*. 2014;13(6):685-696.