The conventional APS treatment including aspirin and low-molecular-weight heparin combination is effective in approximately 70% of pregnancies that are improved using this regimen, but almost 30% of patients (refractory APS) are still unable to give birth to healthy neonates despite this conventional treatment. In the abovementioned PREGNancy in women with ANTiphospholipid Syndrome study, the authors discussed several additional treatments for refractory APS, including corticosteroids, plasma exchange, and intravenous immunoglobulins.

However, it is surprising that hydroxychloroquine (HCQ) was not cited in the study by Saccone et al.[1]

Currently HCQ is an important additional treatment for refractory APS,[2-4] acting in antithrombotic activities, and as an antiinflammatory agent, reducing the antiphospholipid antibody (aPL) bindings to syncytiotrophoblasts, restoring annexin A5 expression, and antagonizing the aPL mediate inhibition of trophoblast migration, invasion, and differentiation.

In addition, the inhibition of lysosomal enzymatic function is hypothesized to be one of the causes of HCQ beneficial effects. HCQ inhibits the lysosomal degradation of mucopolysaccharides and proteins by inhibiting major histocompatibility complex class II–dependent antigen processing and presentation by monocytes. This process decreases the antigen binding to the surface of the professional antigen-presenting cells, reducing the number of peptide-major histocompatibility complex class II complexes for transport to the cell surface and presentation to CD4 T cells. Moreover, HCQ inhibits the interaction of memory B cells, but not unprimed B cells specific for foreign antigens, and modulates some steps in the synthesis and metabolism of interleukin-1. Both these mechanisms result in the inhibition of the generation of immunoglobulin-secreting cells. Therefore, there are 2 consequences of these mechanisms: the reduction in production of autoantibodies and the nonactivation of the complement system.

HCQ has been shown to have an important role to improve pregnancy outcome[4] and to reduce the antiphospholipid antibodies title.[2]

In conclusion, we aim to highlight the importance of the use of HCQ as additional treatment in patients with refractory APS. For the future, the beneficial effect of HCQ in high-risk-profile APS patients, as women showing triple aPL positivity, or in the treatment of APS will be clarified by further studies. ■

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REPLY

We thank Dr De Carolis et al for their interest in the PREGNancy in women with ANTiphospholipid Syndrome (PREGNANTS) study.[1] PREGNANTS is a multicenter cohort study of women with primary antiphospholipid syndrome (APS) referred to 7 Italian university hospitals. Strict inclusion criteria were used. Only women treated with both low-dose aspirin and prophylactic low-molecular-weight heparin (LMWH) were included. Those who received other therapies, including hydroxychloroquine, were intentionally excluded to provide a homogenous study group.

The best treatment of women with APS is still a subject of debate, and several therapies have been studied.[2] Treatment with hydroxychloroquine has been evaluated in a few observational nonrandomized studies, and the observations suggest that this therapy may improve pregnancy outcomes beyond that observed with LMWH and aspirin. However, because the efficacy in singleton gestations with primary APS and without systemic lupus erythematosus has not been proved in an appropriately powered randomized trial,[3] its use is not currently recommended by guidelines.[1]

In the PREGNANTS study, of the 1201 primary APS pregnant women screened for the inclusion criteria, 19 (1.6%) were excluded because they also received other therapies. This means that clinicians feel uncomfortable using other therapies[4] if not recommended by international guidelines[2] and if efficacy is not supported by level 1 data. We fully support randomized controlled trials of

hydroxychloroquine for the treatment of APS in pregnancy in addition to LMWH and low-dose aspirin. ■

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