Response to: 'Protective effects of antimalarials in Chinese patients with systemic lupus erythematosus' by Wang *et al*

In their letter, Wang *et al*[1] present further data showing impressively the beneficial effects of antimalarials and in particular hydroxychloroquine (HCQ) in patients with systemic lupus erythematosus. They refer to our article on the interference of HCQ with proinflammatory signalling pathways.[2] We showed that HCQ prevents activation of endosomal NADPH-oxidase (NOX) by cell surface receptors, for example, the receptors for tumour necrosis factor α (TNFα) or interleukin-1β (IL-1β). Since signalling of both receptors is mediated in large part but not exclusively by endosomal NOX, HCQ can be regarded as an inhibitor of TNFα and IL-1β. While we would like to agree with Wang *et al* that this pharmacological effect of HCQ may be an explanation of its therapeutic efficacy, their data do not provide any clue to the potential mechanisms of the observed effects. Numerous other potentially beneficial properties of HCQ have been described in the past.[3] Recently, Schreiber *et al* reported in a small cohort of patients with the antiphospholipid syndrome that treatment with HCQ for 3 months significantly reduced the amount of soluble tissue factor (TF) in plasma.[4] Since TF can be induced by antiphospholipid antibodies directly by activation of endosomal NOX[5] or indirectly via TNFα, this provides some indirect evidence that inhibition of endosomal NOX may be relevant in vivo in humans. Interestingly, beneficial metabolic effects of HCQ have been described including lowering of low-density lipoprotein cholesterol and improving insulin resistance.[6] The latter effect would be compatible with an anti-TNFα effect of HCQ. In summary, having identified many pharmacological effects of HCQ, we now need to understand which of them is responsible for the improved patient outcome. This will require clinical studies focused on the different known targets of HCQ.

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