Antimalarial use and arrhythmias in COVID-19 and rheumatic patients: a matter of dose and inflammation?

We read with great interest the paper by Graef and colleagues, 'Festina lente: hydroxychloroquine, covid-19 and the role of the rheumatologist'.[1] As the authors correctly point out, despite firm evidence that their efficacy and safety are lacking,[2] antimalarials are being widely prescribed for the treatment of patients with COVID-19. This, as also underlined with some concern by the European League Against Rheumatism President Iain McInness,[3] has rapidly led to antimalarial supply shortages worldwide, primarily affecting patients with rheumatic disease, such as those with systemic lupus erythematosus and rheumatoid arthritis (RA). In these groups, low-dose antimalarials (hydroxychloroquine up to 6 mg/kg/day and chloroquine up to 4 mg/kg/day) are the mainstay to control immunological response and to prevent flare in view of their favourable efficacy and safety profile.

However, electrophysiological experiments in isolated cardiac preparations and animal models, and some case reports in rheumatic patients, have reported a proarrhythmic effect of antimalarials. Arrhythmias, potentially triggered by hypoxia, metabolic/electrolyte derangement and viral myocarditis, have been reported in 16.7% of hospitalised patients with COVID-19.[4] While this suggests that antimalarial use may further augment the risk of fatal arrhythmias in patients with COVID-19, the evidence supporting this link is currently limited. In a recent retrospective study in 368 hospitalised patients with COVID-19, the use of high-dose hydroxychloroquine was associated with an excess of all-cause mortality compared with standard supportive measures (adjusted HR, 2.61).[5] Moreover, in a parallel phase II trial in severely ill patients with COVID-19, the use of high-dose chloroquine, especially in combination with antivirals and azithromycin, was associated with higher prevalence of QT in lead II corrected with Bazett's formula (QTc)>500 ms compared with low-dose chloroquine (18.9% vs 11.1%).[6] These data are in contrast with those of the WHO, which failed to show a higher risk of sudden death with antimalarials, despite the hundreds of millions of doses given for the treatment of malaria worldwide.[7]

The lack of consensus regarding the proarrhythmic effects of antimalarials in different patient groups, and whether there is a dose–effect relationship, mandates, as clearly stated by Graef and colleagues,[1] robust prospective studies that also account for relevant clinical and demographic characteristics.

Pending the conduct of such studies, we assessed the QT interval in a real-life consecutive series of patients with RA treated with low-dose hydroxychloroquine versus other disease-modifying antirheumatic drugs (DMARDs), with mild to moderate disease, low inflammatory burden and no previous cardiovascular events, enrolled in the Endothelial Dysfunction in Rheumatoid Arthritis study (ClinicalTrials.gov, NCT02341066).[8] Barring C reactive protein, there were no significant between-group differences in clinical and demographic characteristics. Patients treated with low-dose hydroxychloroquine (mean dose 331±95 mg/day) for more than 6 months had a longer QTc and a higher prevalence of prolonged QTc. However, their mean QTc, 420 ms, is within normal limits and, more importantly, the prevalence of QTc>500 ms was very low and not significantly different between patients taking low-dose hydroxychloroquine and those taking other DMARDs (table 1). This suggests that low-dose hydroxychloroquine is unlikely to be proarrhythmic 'per se' and that other factors might predispose severely ill patients, including patients with COVID-19, to malignant arrhythmias.

Table 1 Demographic, clinical and electrocardiographic parameters in patients with RA receiving low-dose hydroxychloroquine or other DMARDs

	RA treated with hydroxychloroquine (n=104)	RA treated with other DMARDs (n=541)	P value
Age (years)	61.0±9.2	60.6±9.5	0.715
Disease duration (months)	114±103	129±116	0.210
DAS-28ESR	3.61±1.38	3.66±1.38	0.743
HAQ	0.75±0.6	0.77±0.6	0.866
CRP (mg/dL)	1.08±2.4	2.02±6.1	0.009
ESR (mm/hour)	26.2±20	27.5±22	0.599
HR (beats/min)	70.1±8.1	69.2±9.9	0.438
QTc (ms)	420.3±30.8	410.6±28.7	0.002
QTc, prolonged, n (%)	10 (9.6)	24 (4.4)	0.030
QTc, >500 ms, n(%)*	0	2 (0.4)	1
K+† (mEq/L)	4.1±0.3	4.1±0.3	0.862
Ca++† (mg/dL)	9.2±0.4	9.1±0.4	0.752

*Fisher's exact test.
†Available in 150 subjects. Values are mean ±1 SD.
CRP, C reactive protein; DAS28-ESR, Disease Activity Score 28-joints measured with erythrocyte sedimentation rate; DMARD, disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; HR, heart rate; QTc, QT in lead II corrected with Bazett's formula; RA, rheumatoid arthritis.

Among such factors, the presence of high-grade systemic inflammation, through the release of the proinflammatory cytokine interleukin (IL)-6, has been shown to predispose to QTc prolongation via the inhibition of the rapidly activating repolarising K+ current.[9] Of note, the use of tocilizumab, an IL-6 receptor blockade approved for the treatment of cytokine release syndrome, has been shown to reverse QTc prolongation. High-grade systemic inflammation might lower the arrhythmic threshold both in rheumatic patients with high disease activity and in patients with severe COVID-19, increasing the risk of malignant arrhythmias with antimalarials, particularly at high doses.

Collectively taken, these observations suggest that (1) the risk of clinically relevant arrhythmias with antimalarials, although negligible at low, 'rheumatological' doses, may be different with higher dosages; (2) QTc screening and monitoring should be encouraged in patients taking high-dose antimalarials, particularly when combined with other QT-prolonging medications; and (3) the prompt and aggressive control of inflammation may be helpful to reduce the arrhythmic risk in severely ill patients.

In conclusion, pending the generation of robust evidence of efficacy and safety in patients with COVID-19 and given their acceptable safety profile at low doses, we strongly believe that every possible effort should be made to ensure sufficient supply of antimalarials to rheumatic patients, a large group that continues to depend on these agents for disease activity control.[1–3]

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Collaborators GF conceived the original idea. GLE, ESF, MP, EG and GP contributed to methods of data collection, patient materials and data management. GLE, AM, ESF and GF wrote the manuscript. All authors reviewed, discussed and helped interpret the findings, commented on and approved the final version of the manuscript.

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Funding Data presented in this work are a part of the EDRA study (Endothelial Dysfunction Evaluation for Coronary Heart Disease Risk Estimation in Rheumatoid Arthritis study). ClinicalTrials.gov: NCT02341066. The EDRA study is a project funded by the Italian Ministry of Health and by the Regione Sardegna (RAS): GR- 2011-02352816, Ricerca Finalizzata 2011.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Erre GL, Ferraccioli ES, Piga M, *et al*. *Ann Rheum Dis* 2021;**80**:e29.

Received 1 May 2020
Accepted 2 May 2020
Published Online First 18 May 2020

Linked

► http://dx.doi.org/10.1136/annrheumdis-2020-217923

Ann Rheum Dis 2021;**80**:e29. doi:10.1136/annrheumdis-2020-217828

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