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PERSPECTIVE

IL-6 (Interleukin 6) Blockade and Heart Rate Corrected QT Interval Prolongation in COVID-19

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The recently published Multi-Society Document from American Heart Association/American College of Cardiology/Heart Rhythm Society by Roden et al[1] conveys an important alert on heart rate corrected QT interval (QTc) prolongation and Torsades-de-pointes risk associated with exploratory coronavirus disease 2019 (COVID-19) treatments. Indeed, accumulating evidence indicates that COVID-19 patients are burdened by a higher risk of malignant ventricular arrhythmias, with a potential contributing role of repurposed antiviral therapies.[1,2] In particular, the authors underlined as among the exploratory COVID-19 treatments are included antimalarials (chloroquine and hydroxychloroquine), protease inhibitors (lopinavir/ritonavir), and azithromycin,[1] all drugs listed as definite or possible causes of Torsades-de-pointes at https://www.crediblemeds.org.

In this view, recommendations about electrocardiographic/QTc monitoring along with a decisional guide for optimizing risk/benefit ratio when exploratory drugs are administered is of crucial importance.[1] Moreover, the document also highlights as severely ill patients with COVID-19 are frequently burdened by comorbidities, specifically electrolyte imbalances, concomitant QT-prolonging drugs, and the high-grade systemic inflammatory state,[1–3] further increasing Torsades-de-pointes susceptibility.[1]

However, while correcting hypokalemia and hypomagnesemia is recommended, the possibility of targeting inflammation to reduce arrhythmia risk has not been addressed, although supported by several data: (1) cytokine levels, particularly IL-6 (interleukin 6), are markedly elevated in severe COVID-19, where the anti-IL-6 receptor monoclonal-antibody tocilizumab seems to be able to reduce mortality[2]; (2) it has been demonstrated that IL-6 directly blocks the human-ether-a-go-go-related potassium channel[2] and that high circulating IL-6 levels (≥10 pg/mL) due to different inflammatory diseases associate with QTc prolongation and Torsades-de-pointes development[3]; (3) IL-6 can also potently inhibit cytochrome p450-3A potentially increasing bioavailability of several QT-prolonging drugs (macrolides, azole antifungals, antidepressants, and antihistamines), as well as induce central hypothalamus-mediated cardiac sympathetic system hyperactivation, a well-recognized trigger for life-threatening arrhythmic events in patients with long-QT syndrome[2]; (4) in active rheumatoid arthritis, tocilizumab rapidly reversed QTc prolongation by controlling systemic inflammation.[4]

A recent study performed on a large cohort of hospitalized patients in the New York City area supports the inherent relevance of these mechanisms in COVID-19. In fact, at admission, that is, before treatment with exploratory antiviral drugs, a high percentage of patients who underwent ECG showed marked QTc prolongation, >500 ms (6.1%, 260/4250), along with elevated C-reactive protein levels (median 13.0 mg/dL).[5]

As a complement to the Multi-Society Document,[1] we propose the perspective to consider administration of anti-IL-6 targeted drugs (tocilizumab and sarilumab) in COVID-19, not only in patients with signs of multi-organ dysfunction, but also in those with QTc>500 ms, particularly when IL-6≥10 pg/mL (Figure). In these subjects, by specifically dampening inflammation-driven arrhythmic risk, IL-6 blockade could reduce the need of withholding/withdrawing potentially useful COVID-19 repurposed pharmacotherapies. Although it is not currently known how to select patients in whom correction of QTc prolongation will improve overall outcome,

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Nonstandard Abbreviations and Acronyms

COVID-19	coronavirus disease 2019
IL-6	interleukin 6
QTc	heart rate corrected QT interval

nevertheless evidence indicates that a short-term anti-IL-6 treatment is safe, also potentially decreasing the extent of myocardial injury frequently observed in COVID-19. A phase II clinical trial evaluating for the first time the impact of tocilizumab in nonrheumatoid arthritis subjects with an acute cardiac damage demonstrated how in these patients, a single administration of tocilizumab reduced the inflammatory response and myocardial injury (troponin levels), with no safety concerns (including infections) in the following 6 months follow-up period.[2]

ARTICLE INFORMATION

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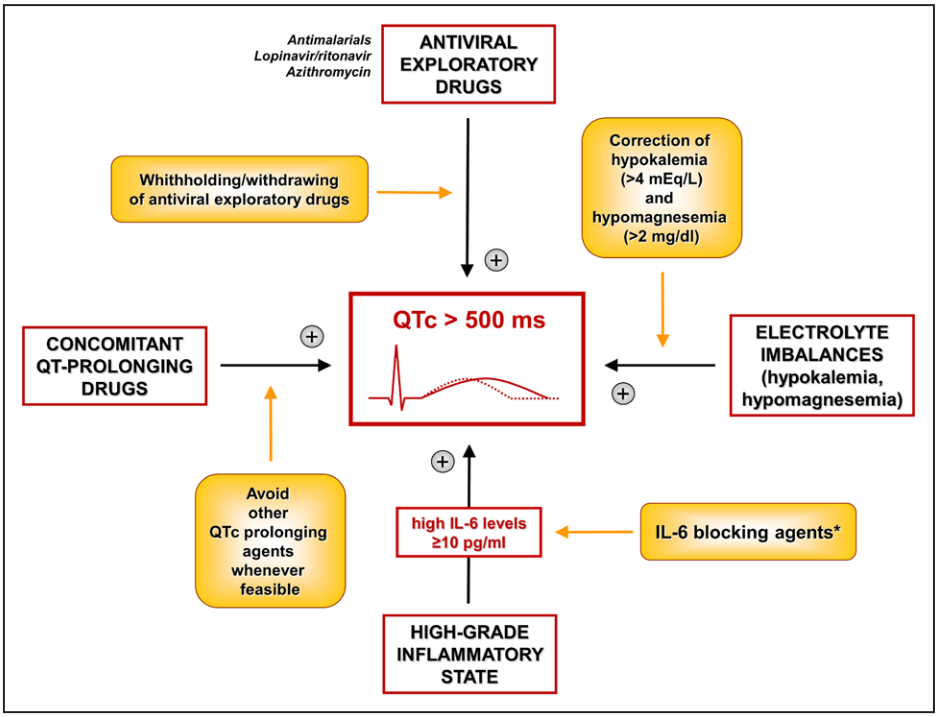

Figure. Proposal for an integrated management of heart rate corrected QT interval (QTc) prolongation in coronavirus disease 2019 (COVID-19), also including inflammation targeting with IL (interleukin)-6 blocking agents.
Yellow boxes represent methods to reverse the mechanisms that related arrows point. *When all other more conventional reversible causes are addressed.