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THERAPEUTICAL POTENTIAL OF ENZYME REPLACEMENT: NEW INSIGHTS AND PERSPECTIVES IN HUMAN ENDOTHELIAL CELLS TREATED WITH CHLOROQUINE

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BACKGROUND AND AIMS: COVID-19 is a pandemic with no end in sight. There is only one approved antiviral agent but global stocks are deemed insufficient. Despite in vitro antiviral activity, clinical trials of chloroquine and hydroxychloroquine were disappointing, and they may even impair outcomes. Chloroquine causes zebroid deposits reminiscent of Fabry disease (α-galactosidase A deficiency) and endothelial cells are key targets of COVID-19. The study aims to investigate in vitro the effect of enzyme replacement therapy (ERT) in chloroquine-induced endothelial dysfunction.
METHOD: We have explored the effect of chloroquine on cultured endothelial cells and its modulation by recombinant α-galactosidase A (agalsidase-β). Following dose-response studies, 0.5 μg/mL chloroquine was added to cultured human endothelial cells. Neutral red and Lysotracker were used to assess lysosomes. Cytotoxicity was evaluated by the 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide) - MTT assay and cell stress by assessing reactive oxygen species (ROS) and nitric oxide (NO). In endothelial cells, chloroquine induced dose-dependent cytotoxicity at in vitro test concentrations for COVID-19 therapy.
RESULTS: Chloroquine significantly induced the accumulation of acid organelles ($P<0.05$), increased ROS levels, and decreased NO production ($P<0.05$), in vitro. These adverse effects of chloroquine on endothelial cell biology were decreased by agalsidase-β ($P<0.05$).
CONCLUSION: Chloroquine-induced endothelial cell cytotoxicity and stress is attenuated by agalsidase-β treatment. This suggests that endothelial cell injury may contribute to the failure of chloroquine as therapy for COVID-19 and may be at least in part related to causing dysfunction of the lysosomal enzyme α-galactosidase A.