

LETTER**Further aspects of doxycycline therapy in COVID-19**

Dear Editor,

In their work, Conforti et al urge experts to broadly investigate the combination of doxycycline and hydroxychloroquine in treating coronavirus disease (COVID-19).¹ The tetracycline antibiotic doxycycline is a nontoxic inhibitor of mitochondrial biogenesis and cellular respiration² besides other known pleiotropic properties.¹ Now that the World Health Organization has just halted hydroxychloroquine trials for COVID-19 because of safety reasons, the time has come to find auxiliary compounds so as to give additional benefit to doxycycline.


We also need to take into account that quite a lot of similarities in metabolic pathways of virally infected and cancer cells have been observed.³ Viruses usually target mitochondria as cellular power houses and various interplays have been detected between viruses and mitochondrial dynamics.⁴ Most viruses require aerobic glycolysis as the energy source for replication and its inhibition could attenuate this process.⁴

Vitamin C is a broad-spectrum antiviral agent⁵ and an inhibitor of aerobic glycolysis.² The combined administration of doxycycline with vitamin C resulted in a robust eradication of cancer stem cells (CSCs) in *in vitro* experiments by blocking mitochondrial protein translation and ATP production from glycolysis.² The addition of azithromycin further boosted CSC clearance.²

Sargiacomo et al also proposed the use of doxycycline or azithromycin in COVID-19.⁶ Their concept assumes that SARS-CoV-2 prefers chronologically aged, senescent lung cells for binding and replication causing stormy inflammation and subsequent fibrosis, suggesting the application of senolytic drugs such as doxycycline to prevent fibrotic transformation.⁶

I believe that a combined approach regarding CSC elimination² may be transmissible into antiviral therapy. Supplementation of doxycycline with the amplifier vitamin C may result in mitochondrial damage of virally compromised cells, the attenuation of immune response by the inhibition of glycolysis in pro-inflammatory immune cells,⁷ and a stronger suppression on postinflammatory fibrosis⁸ than with doxycycline alone.

In vitro very low concentration of doxycycline is able to block mitochondria,² and this antiinflammatory dose is approved up to a 12-month use in rosacea⁹ so a prolonged course together with vitamin C may also be an inexpensive, safe, and promising approach in antiviral prophylaxis and treatment.

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