# Nitazoxanide with hydroxychloroquine in patients with enhanced risk for severe COVID-19 infection

SARS-CoV-2 disease pathogenesis is multidimensional owing to both direct viral infection and host CD8+ T-cell immune response.[1] In SARS, cell-mediated immunity, especially CD8+ T-cell response, is responsible for host damage, including acute respiratory distress syndrome (ARDS) and multiorgan failure.[1] Designing drug therapies based on viral biology and host immune responses, as well as the interplay between them, will enable a targeted approach against SARS-CoV-2 infection. An ideal therapy regimen should (*i*) target and reduce viral replication; (*ii*) upregulate host innate immune antiviral responses; and (*iii*) downregulate the virus-induced immune dysregulation that leads to lung damage and cytokine storm involved in the pathogenesis of ARDS and multiorgan failure.[1]

Nitazoxanide (NTZ) is an antiprotozoal drug that is Food and Drug Administration-approved for treating *Cryptosporidium* and *Giardia*, and has an excellent safety record for variety of indications.[2] It has demonstrated and proven broad antiviral activity. Indeed, NTZ amplifies cytoplasmic RNA sensing and augments type I IFN antiviral responses. It has been shown to have antiviral activity against several viruses including Ebola, hepatitis B and C, rotavirus and norovirus.[3] With regard to respiratory viral infections, NTZ was evaluated in uncomplicated influenza and demonstrated a reduction in median time to symptom recovery.[4] By contrast, it failed to show benefit in hospitalised patients with severe influenza, suggesting that, as with oseltamivir (Tamiflu), it likely needs to be given early in the course of the disease.[5] NTZ has also demonstrated *in vitro* activity against SARS-CoV-2.[6]

Hydroxychloroquine, a drug with a good global safety profile, has been shown in several studies to have antiviral properties (it prevents the virus binding to human epithelial cells and interrupts viral replication). It has direct SARS-CoV-2 antiviral effects in *in vitro* studies, and in early clinical trials has been associated with a reduction in viral load. Several clinical trials are ongoing, but almost all of these studies are or have investigated hydroxychloroquine late in the course of COVID-19 (i.e. in patients who have been hospitalised or who are already receiving respiratory support). Perhaps if hydroxychloroquine is given early in the disease, or in combination with other antiviral drugs such as NTZ, it might prove to be effective. Padmanabhan[1] proposes that combining hydroxychloroquine and NTZ for treatment of COVID-19 is likely to have synergistic activity against SARS-CoV-2, acting against distinct pathways. Hydroxychloroquine reduced viral replication, reduced viral entry (by interfering with ACE2 glycosylation) and has sustained immunomodulatory properties, given its long half-life. However, there is no effect on interferon production, which is inhibited by SARS-CoV-2. NTZ upregulates the interferon innate immune pathway, thus disturbing viral replication.

Thus the proposed treatment regimen with hydroxychloroquine and NTZ will (*i*) diminish the severity of illness by reducing viral titers; and (*ii*) rescue the innate immune system dysregulation brought about by the viral infection. This will reduce the high mortality in the older vulnerable population, thereby allowing our healthcare system a more controlled disease response.

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