

# COVID-19: Older drugs for a novel disease—Chloroquine, hydroxychloroquine, and possible Pentoxifylline—set to start the second innings?

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## ABSTRACT

Currently no drug is approved for the prophylaxis and management of COVID 19. Lots of activities on vaccine and trials with drugs are underway. Some evidence have shown positive results using older established drug in the management of severe cases. We are also of same view and opinion to adopt some emergency measure by pharmacological intervention till a newer drug available in the market.

**Keywords:** Chloroquine, COVID-19, oseltamavir, pentoxifylline

## Introduction

The world tuned into a panic mode after the emergence of the Novel Coronavirus in Wuhan, Hubei Province, China in December 2019. The World Health Organisation (WHO) officially named the new coronavirus infection disease as “Corona Virus Disease 2019, COVID-19” on February 11, 2020. It declared the virus a “global health emergency” in late January 2020. On March 11, 2020, the WHO declared the coronavirus outbreak a pandemic.<sup>[1]</sup>

These corona viruses constitute a larger family of viruses that is common for both pathology of animals and humans.

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This novel coronavirus also called the SARS-CoV-2 presents with the signs and symptoms similar to the earlier breakouts like SARS-CoV (2003) and the MERS-CoV (2015). But the COVID-19 is spreading at a faster pace than its predecessors the SARS-CoV and MERS-CoV and has infected more than 1,00,000 people all over the world as of today.<sup>[2]</sup> Evidences show that the COVID-19 can be transmitted to other people by pre-symptomatic or mildly ill people making it spread at a faster pace.<sup>[3]</sup> Hence there is a need to treat the infected people at an early stage to break the cycle of transmission.

The WHO has issued strategies to control the spread of the infection by non-pharmacological methods, but yet to release a standard treatment protocol to treat the COVID-19.<sup>[4]</sup> The Ministry of AYUSH, Government of India has released the strategies to control and prevent the spread of the COVID-19.<sup>[5]</sup> The strategies released by the Ministry

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of AYUSH are precautionary and prophylactic methods. *Any development of new drugs against the disease will take time which is what we don't have right now.*

Studies of yesteryears have shown that the age-old drug Chloroquine, a 4-aminoquinoline has antiviral actions along with its antimalarial and anti-inflammatory actions. Chloroquine reduces the hospital stay and improve the prognosis during the treatment of the coronavirus infection. It is cheaper and easily available in the market. Hence chloroquine can be considered as a treatment option for treating the novel coronavirus infection.

Rays of hope have arisen as reports of successfully treating a patient of COVID-19 from Rajasthan, India came into news amidst all the negative news.<sup>[6]</sup> According to the reports, a group of Italian tourists landed in India tested positive for COVID-19. Among them one female patient who tested positive earlier turned negative after treatment with a cocktail regimen of anti-HIV drugs Lopinavir and Ritonavir, anti-influenza drug Oseltamavir and antimalarial drug Chloroquine. The same cocktail regimen is being administered to her husband who is under non-invasive ventilatory support. According to the treating physicians, the condition of the patient is stable. The delay in his recovery is vowed to be due to the lung condition which he was already suffering from.

India's research institute of excellence namely the Indian Medical Research Council (ICMR) recently has come out with a treatment protocol for COVID-19 with stringent inclusion criteria.<sup>[7]</sup> Very recently an article concluded that there is no benefit observed with lopinavir-ritonavir treatment as efficacy beyond the routine standard care of management in hospitalized adult patients with severe Covid-19.<sup>[8]</sup>

Another age old drug which we propose for considering in the treatment of COVID-19 is Pentoxifylline. Similar to chloroquine, Pentoxifylline also has antiviral and anti-inflammatory actions which will be beneficial in the treatment of the novel coronavirus.

Hence we focus upon the treatment strategy of the novel coronavirus with the already available drugs like the Chloroquine and Pentoxifylline instead of waiting for a novel drug in particular to the severe cases. The main purpose of this article is that the *“primary care physician should be aware about the fact of using these drugs, their rationale and possible adverse and contraindications”*. Even though the malarial drugs have been used for several decades and the primary care physicians are the frontliner in treating malaria, the knowledge in case of its usage in COVID-19 will help in clarification of the queries raised by the patients also.

### Chloroquine Antiviral Action

Chloroquine belongs to the 4-aminoquinoline group of drugs. It is being used in the prophylaxis and treatment of malaria. It also has good immunomodulatory activity and used in the treatment of various autoimmune diseases like rheumatoid arthritis (RA), systemic lupus erythematosus (SLE). Chloroquine

being a weak base gets concentrated in the acidic vesicles like the lysosomes, Golgi vesicles, and endosomes. The chloroquine once inside the acidic vesicles increases the pH of the vesicles and disrupt the structure of the vesicles.<sup>[9]</sup> The rise in the pH of the vesicles disrupts the enzymes involved in protein synthesis. This, in turn, interferes in the replication of cellular DNA. Many in-vitro and in-vivo studies have shown various mechanisms by which chloroquine exerts antiviral activity on various viruses.<sup>[10-17]</sup> They act by changing the endosomal pH (inhibits viruses such as the avian leucosis virus, Bornavirus, and the Zika virus), inhibiting the viral gene expression by inhibit the replication of the virus, by changing the glycosylation pattern of HIV-1 gp 120 envelope and thereby inhibiting its replication and by inhibiting the autophagy. Vertical transmission of Zika virus from the mother to the fetus may be cut off by Chloroquine that was shown in animal experiments. Chloroquine has proved to have significant antiviral activity against many of the viruses, including the SARS virus in various in-vitro experiments and trials. But when similar experiments were tried in-vivo, the antiviral activity of chloroquine was not significant as compared with those of the in-vitro studies. But, in a recent study from China chloroquine was used in more than 100 patients of COVID-19 with severe pneumonia.<sup>[18]</sup> They have demonstrated that chloroquine was found to be superior in inhibiting the pneumonia exacerbation that was seen positive in improvement in lung Images. They also concluded that it promoted for early viral negative conversion that helped in the shortening of the the disease.<sup>[18]</sup>

Keyaerts *et al.* 2004,<sup>[14]</sup> observed that chloroquine inhibits the replication of SARS in the Vero E6 cells. The study conducted by Xu *et al.* 2020<sup>[19]</sup> compared the structures of SARS and SARS-CoV2. The results were encouraging which showed that both the viruses shared similarities in structure and the Van der Waal forces bonding. The above two studies further encourages the addition of the age old antimalarial chloroquine for COVID-19. In China, more than 10 clinical trials are underway that have included chloroquine for treatment of COVID-19.<sup>[20]</sup> The Guangdong provincial science and technology department has released the expert consensus on chloroquine phosphate for new coronavirus pneumonia<sup>[21]</sup> which has included chloroquine phosphate in the treatment regimen of COVID 19.

Another salts of chloroquine, hydroxychloroquine in a non-randomized study conducted has shown a remarkable disappearance or reduction of the viral load when combined with antibiotic Azithromycin in COVID-19 positive patients.<sup>[22]</sup> It was also inferred that more than 50 clinical trials are registered to check the efficacy of hydroxychloroquine in the treatment strategy of COVID.<sup>[23]</sup>

### Pentoxifylline for COVID-19

Pentoxifylline, is a methyl-xanthine which inhibits Phosphodiesterase-4 (PDE 4). It is approved by the food and drugs administration (FDA) for the treatment of intermittent claudication in patients of chronic occlusive arterial disease of the

limbs.<sup>[24]</sup> The PDE 4 is the regulator of the cyclic AMP (cAMP) metabolism which is involved in the proinflammatory action. Pentoxifylline exerts anti-inflammatory action by inhibiting the cAMP metabolism which in turn reduces the production of the proinflammatory cytokines, the TNF-alpha and INF gamma. This increase in the cAMP is the reason for the bronchodilatory action of pentoxifylline.<sup>[25]</sup> The antiviral activity of this drug is due to the down regulation of the NF kappa B and the NFAT transcription factors which are necessary for the viral replications.<sup>[25]</sup> Studies of Russian scientists demonstrate the in-vitro antiviral activity of pentoxifylline against many viruses including the acyclovir resistant herpes simplex virus, vaccinia virus, rota virus, the tick-borne encephalitis virus, the Japanese encephalitis virus, and the West Nile virus.<sup>[26]</sup>

In a randomized controlled trial conducted by Ardizzoia *et al.*,<sup>[27]</sup> where the effect of pentoxifylline and standard care combination was compared with the standard care of cancer patients with respiratory distress syndrome, the patient group with pentoxifylline were observed to have improvement in the symptoms without any toxic effects.

As the COVID-19 damage the lung which eventually lead on to acute respiratory distress, pentoxifylline with the anti-inflammatory action, which helps in the improvement of ARDS and antiviral activity may be considered as one of the “ideal candidates” for the treatment of COVID-19.

## Conclusion

The antiviral and anti-inflammatory actions of the two age old drugs, the chloroquine<sup>[28]</sup> and the pentoxifylline, along with their immunomodulatory effect, make them a good choice for considering these drugs in the treatment of the COVID-19. In addition both the drugs are inexpensive, easily available with minimum side effects make them ideal to be considered as adjuvant drugs in combination with the proposed antiviral drugs. The anti-inflammatory and immunomodulatory actions of these drugs could play an important role in the treatment of the respiratory distress due to the COVID 19.

## Key points

1. Currently there is no approved standard WHO or ICMR pharmacological treatment options for COVID-19
2. With available scientific evidences from other parts of the world, Chloroquine and hydroxychloroquine could be used with all necessary cautions based in its mechanisms
3. Pentoxifylline is hypothesized for the same with possible mechanism of action
4. Essential knowledge by the family primary care physician regarding Chloroquine/hydroxychloroquine is highly mandatory in time of [andemic and panicity
5. QTc should be evaluated by the primary care physician before prescribing chloroquine or hydroxychloroquine in case of treatment or prophylaxis.

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## Conflicts of interest

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