

EFFECT OF INTERFERON ALFA AGAINST CORONAVIRUS

- Due to its known mechanism of action, Interferon has been commonly used against viral infections for which there are no specific therapies available.
- The antiviral effect of interferon has been extensively demonstrated being the first line of antiviral defense, activating both the innate immune response against the virus as well as the mechanism of inhibition of viral replication due to the Interferon inducer genes (W.M. Schneider, et al. *Annual Review of Immunology*. **2014**; 32:513-545).
- It has been reported that SARS-CoV (Coronavirus associated to 2002 outbreak) reduces IFN expression, avoiding the activation of IFN inducer genes like STAT1 and MyD88 and the possibility for the antiviral defense mechanisms to detect the presence of the virus. (M.J. Cameron, et al. *PLoS ONE* **2012**, 7 (9): e45842).
- The papain-like protease of the coronavirus has shown antagonistic activity to Interferon. Interferon Antagonism Activities of Coronavirus Papain-Like Proteases. *J Virol*. **2010**;84(9):4619-29.
- Both SARS and MERS are antagonistic to interferon. *Advances in Virus Research*. **2016**. p. 219-43.
- It has been demonstrated that Interferon's induction protects against infection caused by MERS-CoV (coronavirus associated to 2012 outbreak). Blockage of Interferon prolongs virus clearance, increases the inflammatory response and decreases the T-cell mediated cellular response.
- Demonstration of the sensitivity of SARS / MERS CoV to Interferon and other drugs based on hyper immune serum in man. *Infect Disord – Drug Targets* [Internet]. **2014** Sep 11 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25019238>
- Has been shown that the induction of NF-kB (associated mechanism with the increase of proinflammatory cytokines) is increased in adult monkeys associated with lung damage, and consequently the inflammatory response mediated by cytokines IL-6 and IL-8. In young monkeys where IFN early expression is elevated this does not happen. (S.L. Smits, et al. *PLoS Pathogens*, 6 (2010), p. e100075).
- The administration of IFN during the first day after inoculating mice with the virus (before the viral multiplication peak is reached), prevented

the death of the mice by producing a subclinical infection. A late administration of IFN did not achieve the same effects.

R. Channappaavar, et al. *J Clin Invest.* **2019**;129(9):3625-3639.

<https://doi.org/10.1172/JCI126363>).

- Recent articles have also shown that early IFN expression enhance the rapid induction of the neutralizing antibody response. (Marco de Giovanni, et al. *Nature Immunology* **2020**).
- It is recommended the use of Interferon in pregnant women using nebulization through the respiratory tract. Review *Acta Obstet Gynecol Scand.* **2020**;00:1-4., article “Novel corona virus disease (COVID-19) in pregnancy: What clinical recommendations to follow?”.
- Recommended use of nebulized Interferon Alfa 2B in children. *World Journal of Pediatrics*, February **2020**, articles “Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts’ consensus statement” and “Pharmaceutical care recommendations for antiviral treatments in children with coronavirus disease 2019”.

These evidences and previous studies suggest the possible use of Interferon as a preventive therapy in a vulnerable population and in early stages of infection. In addition, the use of Interferon in the current pandemic continues to be published and is recommended in Patient Treatment Protocols by different countries and organizations.

Given the urgency to stop the spread of this pandemic, not only interferon, but different drugs are being used as therapeutic tools, even though their efficacy has not been demonstrated for the treatment of SARSCOV-2.

Recommendations on the clinical use of Interferon issued in guidelines by WHO, China, Singapore, South Korea and Spain

- Chinese Society of Pharmacology Experts Consensus issued on February 6, 2020:: Interferon-alpha (adults: 5 MIU diluted in 2ml water for injection and nebulized twice a day)
- Listed on the indications of “Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia”(Trial Version 7) issued by the National Health Commission & State Administration of Traditional Chinese Medicine on March 3, 2020.
- Listed on the Guidelines issued by the John Hopkins Medical Center in Baltimore.
- Listed on the Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID 19), February 16th to 24th. Page 32/33 quote: “There are no specific antiviral or immune modulating agents proven (or recommended) to improve outcomes. All patients are monitored by regular pulse oximetry. The guidelines include supportive care by clinical category (mild, moderate, severe and critical), as well as the role of investigational treatments such as chloroquine, phosphate, lopinavir/ritonavir, alpha interferon, ribavirin, arbidol. The application of intubation/invasive ventilation and ECMO in critically ill patients can improve survival”
- The Interferon was also recommended by the Experts Committee for the Treatment and Prevention of COVID-19 in a recent article published on January 29th in the World Journal of Pediatrics. The Committee was formed by representatives from the Group of Respiriology, Chinese Pediatric Society, Chinese Medical Association, Chinese Medical Doctor Association Committee on Respiriology Pediatrics, China Medicine Education Association Committee on Pediatrics, Chinese Research Hospital Association, Committee on Pediatrics, Chinese Non-government Medical Institutions Association, Committee on Pediatrics, China Association of Traditional Chinese Medicine, Committee on Children’s Health and Medicine Research, China News of Drug Information Association, Committee on Children’s Safety Medication, Global Pediatric Pulmonology Alliance, <https://doi.org/10.1007/s12519-020-00343-7>

The above mentioned article recommends the following treatments:

1. Interferon- α nebulization: interferon- α 200,000–400,000 IU/kg or 2–4 μ g/kg in 2 mL sterile water, nebulization two times per day for 5–7 days
 2. Interferon- α 2b spray: applied for high-risk populations with a close contact with suspected 2019-nCoV infected patients or those in the early phase with only upper respiratory tract symptoms. Patients should use 1–2 sprays on each side of the nasal cavity, 8–10 sprays on the oropharynx, and the dose of interferon- α 2b per injection is 8000 IU, once every 1–2 hours, 8–10 sprays/day for a course of 5–7 days.
- The Spanish Guides issued on the 3rd of March on its recommendation section refer the Chinese experience using interferon α 2b nebulization with the following dosage: 100.000–200.000 UI/kg for mild cases, and 200.000–400.000 UI/kg for severe cases, twice a day during 5 to 7 days.
 - The National University of Singapore (NUS) on its indications issued March 12, 2020, also refers the Chinese experience of the use of interferon in combination with Kaletra (lopinavir/ritonavir)