INTERFERON AND INTERFERON INHIBITORS

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Introduction

Interferons (IFN) are a group of signaling proteins that are produced by host cells early in a viral infection by "interfering" with viral replication and subsequently protect the host cell from viral infections.

Mechanism of Action

Three types of IFNs, types I (IFN-α and IFN-β), II (IFN-γ) and III (IFN-λ), have been classified based on of their genetic, structural, and functional characteristics and their cell surface receptors.[1] IFN-α was produced principally by leukocytes, IFN-β by epithelial cells, fibroblasts and neurons, and IFN-γ by immune cells. IFN-β, however, undergoes switching to become IFN-α during the amplification phase of the immune response.

As part of the host's antiviral innate immune response, type I IFNs stimulate adjacent cells to produce antiviral proteins, inhibit cell proliferation, regulate apoptosis and promote immunomodulation. Such mechanisms decrease the rate of virus multiplication and also facilitate the adaptive immune response.[2]

Type I IFNs (IFN-α/β) signal through a receptor complex and triggers a proinflammatory response via the recruitment and activation of immune cells against viral infections. However, this inflammatory reaction can have serious systemic side effects since the IFN receptor is also expressed on all cells. In contrast, type III IFNs (IFN-λ1-4) signal through a distinct receptor complex, restricted only to epithelial cells and a subset of immune cells, including neutrophils. Therefore, Type III IFN administration as prophylactic treatment in the early stage of COVID-19 would result in an antiviral response localized to epithelial cells, reducing side effects and inflammation.[3] A new long-acting formulation of IFN-α, called pegylated IFN-α, has features that reduces immunogenicity, decreases sensitivity to proteolysis, and lengthens serum half-life.

Studies in animals have shown that SARS-infected cells have low production of interferons. But SARS-CoV remains sensitive to interferons with IFN-β seemingly more potent that IFN-α and IFN-γ.[4] IFN-γ is a pleiotropic cytokine that plays an essential role in multiple phases of immune and inflammatory responses. Although protective in the context of anti-viral host defense, IFN-γ also has been implicated in the pathogenesis of "cytokine storm" and in various autoimmune diseases. Elevated serum interferon gamma has been associated with severe acute respiratory distress in COVID-19.[5] Anti-interferon therapy is approved in the US for the treatment of primary HLH.

Emapalumab, a human monoclonal antibody that binds to binds to soluble and receptor-bound forms of IFN-γ is one of investigational drugs for COVID-19.

Clinical Studies

The IFN response is considered important for the control of coronavirus infection. Interferons have their highest utility in the prophylaxis or early post-exposure management of SARS.[2] In a retrospective cohort study done among pediatric patients with mild to moderate COVID-19, combination interferon alfa aerolization and lopinavir-ritonavir resulted in a complete cure of all 36 patients. Improvement in pneumonia was seen 4–10 days after treatment initiation. SARS-CoV-2 RT-PCR results became negative after a mean of 10 days of treatment and the mean number of days in hospital was 14 days.[6]

In a non-randomized retrospective study, 77 adults hospitalized with confirmed COVID-19 were treated with either nebulized IFN-α2b, arbidol, or a combination of IFN-α2b plus arbidol. Study results showed that treatment with IFN-α2b with or without arbidol significantly reduced the duration of detectable virus in the upper respiratory tract and in parallel reduced duration of elevated blood levels for the inflammatory markers IL-6 and C-reactive protein.[7] Additionally, an open-label non-randomized controlled trial was launched in China to test the efficacy of IFN-α-2b and Lopinavir/Ritonavir versus routine medical treatment in hospitalized patients with SARS-CoV-2 infections.[8] Moreover, there are at least 15 registered clinical trials examining the efficacy of interferons in the treatment of COVID-19 and 1 open label controlled study investigating the efficacy and safety of intravenous administrations of Emapalumab, a monoclonal antibody targeting interferon gamma (Anti-IFNγ), and Anakinra versus standard of care, in reducing hyperinflammation and respiratory distress in patients with SARS-CoV-2 Infection. These studies are either currently recruiting or not yet recruiting. Two studies have completed recruitment but there are no available results yet. Therefore, these findings suggest that IFN should be further investigated as a therapy in COVID-19 cases. (Appendix 11)

Currently in China, the Novel Coronavirus Infection Pneumonia Diagnosis and Treatment Standards (the fourth edition) and Diagnosis, treatment and prevention of 2019 novel coronavirus infection in children: experts' consensus statement listed IFN-α atomization as a choice of treatment for 2019nCoV pneumonia.[9] In adults, the COVID-19 Clinical Practice Guidelines (2020) of the Medical and Health Care Wuhan University Novel Coronavirus Management & Research Team and China International Exchange & Promotive Association for Medical and Health Care recommends IFN- alpha and lopinavir/ritonavir as the antiviral therapy.[10]

As of its last update, there have been eight newly registered clinical trials in the US National Library of Medicine ClinicalTrials.gov website investigating the

effect of interferon in COVID-19 patients, which are either ongoing recruiting or not yet recruiting.

Results of three other clinical trials were already published. Two trials in Iran evaluated the subcutaneous administration of interferon β-1a in COVID-19. A prospective non-controlled trial evaluated the therapeutic effects of subcutaneous IFN-β-1a administration in remission of symptoms of COVID-19. Twenty patients were enrolled and received interferon β-1a as adjunct to conventional therapy, including hydroxychloroquine, and lopinavir/ritonavir. Findings support the use of IFN-β-1a in combination with hydroxychloroquine and lopinavir/ritonavir in the management of COVID-19. Fever resolved in all patients after 8 days while some of the symptoms gradually decreased. Results of the virological clearance showed a significant decrease within 10 days and imaging studies showed significant recovery after 14 days in all patients. Furthermore, no deaths or significant adverse reactions were reported within 14 days[11].

Another study was an an open-label randomized clinical trial which studied the efficacy and safety of subcutaneous administration of interferon β-1a as adjunct therapy to standard of care compared to standard of care alone in treatment of severe COVID-19. The study enrolled 42 patients in the treatment group and 39 patients in the control group. Results showed that time to reach the clinical response did not change between groups but there are significantly increased discharge rates on day 14 (OR= 2.5; 95% CI: 1.05- 6.37), significantly reduced mortality if early administration of IFN initiation (OR=13.5; 95% CI: 1.5-118), more extubations (p=0.019), and decreased 28-day mortality in the treatment group compared to the control group (19% vs. 43.6% respectively, p= 0.015)[12].

A single-center, randomized, open-labeled clinical trial was conducted in China which compared the effectiveness of three antiviral treatment regimens involving inhaled interferon among patients with mild to moderate COVID-19. The study enrolled a total of 101 patients with 33 patients in group 1, 36 patients in group 2 and 32 patients in group 3. The three treatment groups were the following: (1) ribavirin (RBV) plus interferon-a (IFN-a), (2) lopinavir/ritonavir (LPV/r) plus IFN-a, and (3) RBV plus LPV/r plus IFN-a at a 1:1:1 ratio. Results showed that that there were no significant differences among the three regimens in terms of antiviral effectiveness. Furthermore, the authors suggested not to administer RBV and LPV/r simultaneously as it is associated with a significant increase in gastrointestinal adverse events.[13]

Recommended Dose

Population	Preparation	Dose
Pedia[9]	Interferon α nebulization	200,000-400,000 IU/kg or 2-4 μg/kg in 2 ml sterile water, nebulization 2x per day for 5-7 days
	Interferon –α2b spray	*Note: Applied for high risk populations with a close contact with suspected 2019-mCoV infected patients OR those in the early phase with only upper respiratory tract symptoms*

	Interferon –α2b spray	1-2 sprays on each side of the nasal cavity, 8-10 spray on the oropharynx
	Interferon –α2b injection	8000 IU, once every 1–2 h, 8–10 sprays/day for 5–7 days
Adult[14]	Interferon α	5 million units or equivalent dose in 2 ml sterile water via vapor inhalation 2x a day for no more than 10 days
	Interferon β-1a[11]	44ug (12million international units) subcutaneously every other day until day 10
	Interferon β-1a[12]	44ug (12million international units) subcutaneously 3x weekly for 2 consecutive weeks

Adverse Effects

Influenza-like symptoms such as fatigue, headache, fever, myalgia, loss of appetite are the most common side effects of IFN treatment, with a severity dependent on the dosage used. These side effects are usually tolerable and tend to become less severe with time. Other side effects include alopecia, weight loss and mental depression which will prompt discontinuation of treatment. Potentially fatal side effects include hepatotoxicity, development of pulmonary infiltrates, pneumonitis, pneumonia and autoimmune diseases.[15]

In children, IFN-α (> 2 μg/kg/time) could cause myelosuppression. Overdose of IFN-α also could cause liver enzyme abnormalities, renal failure, bleeding. IFN-α is contraindicated in patients with abnormal liver function. In children with creatinine clearance (CrCl) below 50 mL/min, IFN-α is prohibited. IFN-α is also contraindicated in children with histories of mental illness, severe or unstable heart disease, or aplastic anemia. IFN-α nebulization should be used with caution in neonates and infants younger than 2 months. Adverse reactions of IFN-α mainly include low-grade fever and flu-like symptoms (both in children with intramuscularly injection). Growth and development inhibition is more common when combining IFN-α with ribavirin. Suicidal ideation is more common in children (mainly adolescents) compared with adults (2.4% vs. 1%). [16]

Interferon reduces the clearance of theophylline and may enhance myelosuppression with other myelosuppressive drugs such as Zidovudine.

Conclusion

Interferons may have a role in early treatment in coronavirus infections, but more clinical trials are needed to validate this. There is insufficient evidence to conclude its efficacy and safety in the treatment of COVID-19. Use with caution in children.

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