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Interferons and its use in children with COVID-19: a narrative review

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Abstract

Background: All ages, including children, are susceptible to the disease COVID-19. The severity of COVID-19 in children is milder than in adults. One of the recommended antiviral drugs for COVID-19 in children is interferon.

Objective: To describe the efficacy and safety of using interferon in children with COVID-19

Method: The article is a narrative study. The main databases in the article search process in this literature review are PubMed and Google Scholar.

Results: The articles that could potentially be involved in this study were 28 articles. A total of 13 articles included the criteria, 9 articles discussed the use of interferon against respiratory syndrome, 4 articles on interferon in children, and one reference from a literature search.

Conclusion: Interferon therapy in COVID-19 in children has a high cure rate but needs to be evaluated in a larger sample of pediatric patients.

Keywords: Interferon, COVID-19, children

1. Introduction

In December 2019, the Chinese authorities made a preliminary determination of the coronavirus in a person hospitalized with pneumonia in Wuhan Hubei Province. Chinese authorities later reported that laboratory tests ruled out results related to SARS-CoV, MERS-CoV, influenza, avian influenza, adenovirus, and other common respiratory pathogens (WHO, 2020). The virus that causes this disease belongs to the Coronaviridea coronavirus family group that caused two other outbreaks, namely severe acute respiratory syndrome (SARS) in 2002 and Middle East Respiratory Syndrome (MERS) in 2012. This disease has been named by WHO, namely Coronavirus Disease 2019 (COVID-19) (Basha, 2020).

All ages, including children, are susceptible to COVID-19. However, the sample size in available reports on clinical characteristics of children with COVID-19 is usually small. The antiviral drug for COVID-19 in children recommended in the consensus is nebulized interferon especially for children with mild pneumonia. Since most of the children are relatively mild, research tends not to be supported to test the efficacy of this drug on the results obtained (Peng *et al.*, 2020). This article can be used as a reference and consideration for using interferon because it describes the efficacy and safety of using interferon in children with COVID-19.

2. Methods

This article is a narrative study. The main databases in this literature review are PubMed and Google Scholar with keywords: Interferon AND Children OR Infant* OR "Neonate" OR "Child" (coronavirus OR covid* OR "SARSCoV-2" OR "2019-NCov"). All articles published during the last 3 years to November 2020 have the potential to be included in this study. Literature searches used as references in published articles were also carried out as an effort to enrich this study. The inclusion criteria in this study include articles that present qualitative, quantitative, effectiveness, safety, and side effects data that can be used as a reference. The articles excluded in this study were articles over the last 3 years, studies of cellular and molecular mechanisms, animal model studies, and absence of interferon intervention or insufficient data.

3. Results

There were 13 articles that match the inclusion criteria from total 28 articles found. It covers 9 articles that discussed the use of interferon in respiratory syndrome, 4 articles of interferon used in children, and one reference from literature search. The flowchart of identification and the articles showed in Figure 1 and Table 1.

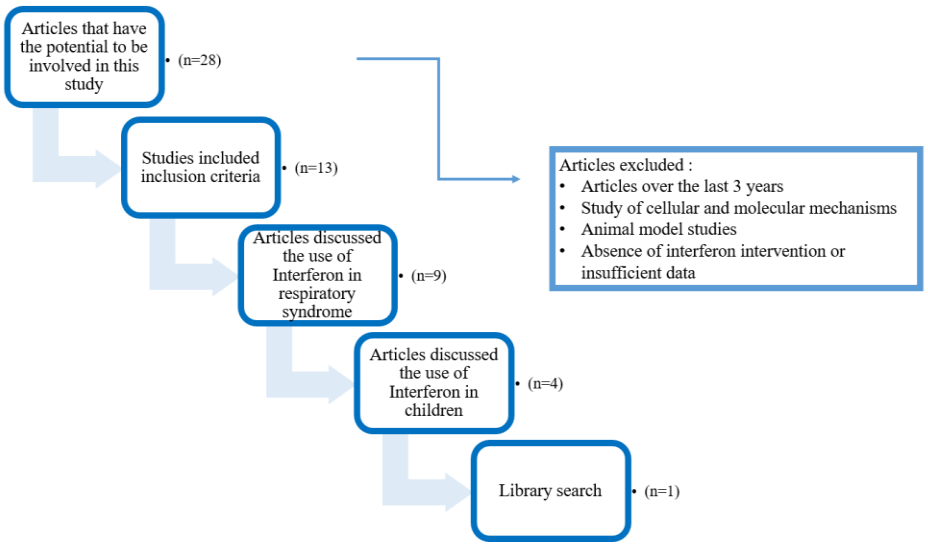

Figure 1. Flowchart of identification and inclusion articles

Table 1. Studies of interferon

No.	Author (year)	Result
1	Jiang *et al.* (2020)	A multicenter, randomized, double-blind, placebo-controlled trial with a total of 163 patients at least 14 years old were included in the complete analysis set (FAS) and 151 patients were included in the per-protocol set (PPS), there were patients in the IFNα1b group and patients in the control group shows that recombinant human interferon α1b (IFNα1b) inhaled aerosol is safe and can improve clinical symptoms of non-influenza viruses.
2	Liu *et al.* (2020)	In critical handling of COVID-19, most of it is a supportive therapy, giving interferon inhalation atomization can help and does not have a mortality rate.
3	Payandemehr *et al.* (2020)	Investigator-initiated, open-label, single-arm clinical trial research in 20 adult patients with suspected COVID-19 supports the use of interferon beta-1a as an adjunct to the antiviral treatment recommended in COVID-19 patients.
4	Peng *et al.* (2020)	Interferon α1b therapy in 75 pediatric COVID-19 patients obtained a 100% cure rate. Most children recover within two weeks.
5	Sallard *et al.* (2020)	Interferon-β1 has mixed efficiency against MERS-CoV and SARS-CoV viruses but in vitro studies have shown that SARS-CoV-2 is substantially more sensitive to interferon-I.
6	Sheahan *et al.* (2020)	Interferon is also used in MERS-CoV. Lopinavir/ritonavir prophylaxis plus interferon-β slightly reduces viral load without affecting other disease parameters and improves lung function.
7	Shen *et al.* (2020)	The use of interferon-α in treating bronchiolitis, viral pneumonia, acute upper respiratory tract infections, hand-mouth disease, SARS, and other viral infections in children. The recommended use of interferon is interferon-α nebulizer and interferon-α2b spray.
8	Shen & Yang (2020)	Inhalation of recombinant human interferon-α2b can effectively reduce the infection rate of respiratory viruses, influenza viruses, adenoviruses and SARS-CoV.
9	Sujaritha *et al.* (2020)	Interferon is safe and comfortable to enhance treatment in the early stages of COVID-19 infection and can protect the respiratory tract.
10	Tidwong *et al*. (2020)	Interferon-α and interferon-β have *in vitro* activity against SARS-CoV and MERS-CoV. Interferon-β showed the strongest *in vitro* inhibition against MERS-CoV.
11	Yellepeddi *et al.* (2019)	Interferon products such as Pegasys® (PEGylated interferon alpha-2a) exhibit 4-fold lower clearance, longer time to steady state, and 25-70% higher AUC in children compared to adults. Meanwhile, PegIntron® (PEGylated interferon alpha-2b) showed about a 50% increase in AUC compared to adults with the same dose.
12	Yu *et al.* (2020)	Interferon type I was well tolerated and did not increase any adverse effects. Interferon type I is therefore recommended as a first-line antiviral for SARS-CoV-2 infection in a local protocol, with timely administration and monitoring of side effects.
13	Zimmermann & Curtis[1] (2020)	In the absence of specific antiviral drugs for CoV the use of broad-spectrum antiviral drugs such as alpha and beta interferon or ribavirin can be used for the treatment of SARS-CoV in children.

4. Discussion

4.1 Clinical and epidemiological conditions of COVID-19 in children

The main clinical symptoms of COVID-19 in children are fever, dry cough, pneumonia and just under a third are asymptomatic. In addition, one fifth had pneumonia and required radiographs for further identification. Symptoms seen in children on admission vary, including cough and fever. All asymptomatic patients and children without pneumonia require laboratory and radiographic examinations for further diagnosis (Qiu *et al.*, 2020). Children can be carriers of this virus. Children with severe clinical symptoms of COVID-19, especially those with pneumonia, should be hospitalized as adults, while mild clinical symptoms require quarantine. In children without clinical symptoms and infection, a home isolation protocol is recommended (Zare-Zardini *et al.*, 2020).

Clinical presentation and outcome are better in children. Most cases and critical occurence of COVID-19 are in the group of children aged less than three years, so they need better attention while being treated in a hospital or children who are cared for at home (Zheng *et al.*, 2020). The clinical characteristics of cases of infected children can be divided into several clinical types, namely asymptomatic, mild, ordinary, and severe infections (Miao *et al.*, 2020). COVID-19 causes asymptomatic to severe illness, but the condition in children without comorbidities and neonates has mild symptoms. There is no specific antiviral drug treatment for neonates and children, therefore neonatologists need more virological, epidemiological, and clinical data for COVID-19 therapy (Lu & Shi, 2020)

Laboratory results in children with COVID-19 are leukocytes are usually normal or reduced with a decrease in the number of neutrophils and lymphocytes, thrombocytopenia occurs, meanwhile levels of C-reactive protein and procalcitonin are often normal. In severe cases, liver enzymes are elevated as well as levels of lactic dehydrogenase, abnormal coagulation, and an increasing level of D-dimers. Chest radiographs of most of the children showed bilateral air space consolidation in the peripheral lungs, peribronchial thickening, and ground-glass opacities. Chest CT predominantly shows airspace consolidation and ground-glass turbidity (Zimmermann & Curtis[1], 2020).

Children are susceptible to SARS-CoV-2 infection even if they do not have a congenital disease. Children can become facilitators of transmission of the virus. If children are important in transmitting the virus, it is advisable to avoid interactions with the elderly to slow

transmission and protect vulnerable populations (Kelvin & Halperin, 2020). Pediatric patients contracted COVID-19 with a clear route of transmissions such as close contact with family members, history of exposure to epidemic areas, or both. No other source of transmissions such as being in a hospital, or an unclear route of transmission was identified. This transmission means that the identification of these pediatric patients is very easy (Qiu *et al.*, 2020). COVID-19 in children is mainly caused by transmission from families with mild symptoms and a better prognosis than in adults. Symptoms in children are difficult to recognize early because the clinical process is mild or without symptoms (Su *et al.*, 2020).

The pattern of transmission of COVID-19 in children is generally similar to that of SARS and MERS. The mean incubation period between household exposure to symptomatic children and the onset of symptoms was 6.5 days which is longer than that observed in the adult case of 5.4 days. This difference suggests that the incubation period is longer in children with 2019-nCoV infection. The accumulation of the virus in the respiratory specimens takes longer in children with mild COVID-19 and 2019-nCoV RNA is not detected in serum samples (Jiehao *et al.*, 2020). The risk of transmission of the virus is lower in children than in adults (1.3 vs. 3.5%), the risk of a child developing a severe illness requiring hospitalization is 25 times lower than in adults (0.1% vs. 2.6%) and the risk of death is 500 times lower than in adults (0.001% vs. 0.5%). Presentation rates should be taken with caution because of possible bias, but it can be concluded that resistance to infection and resistance to disease in children is stronger than in adults (Fisher, 2020). There are several causes that may protect children from SARS-CoV-2 infection compared to adults including differences in innate and adaptive immunity, pre-existing immunity to the coronavirus, and lower intensity of SARS-CoV-2 exposure (Zimmermann & Curtis[2], 2020).

4.2 Overview of interferon

There are four types of interferons, namely alpha interferon, beta interferon, gamma interferon, and lambda interferon. Alpha interferon is also called leukocyte interferon because it is produced by leukocytes, IFN-α is produced by lymphocytes and macrophages due to virus-infected cells. Interferon beta is also called fibroblast interferon because it is produced by fibroblasts and epithelial cells. IFN-ß arises due to the action of foreign nucleic acids such as viruses or other types. Gamma interferon is a subclass of interferon type II. IFN-ɣ is also called

immune interferon. IFN-ɣ is produced mainly by activated lymphocytes or T cells. IFN-ɣ increases macrophage activation, antiviral immunity, and antigen presentation. IFN-ɣ can also regulate activation of the innate immune system and coordinate lymphocyte-endothelial interactions. Lambda interferon is type III interferon. IFN-λ is induced by viruses and other interferons. IFN-λ has in vivo antiviral activity (Kingsley & Peace, 2020).

Interferons are a group of low molecular glycoproteins with a structure and function similar to those produced by the body in response to viruses. Interferons are the body's first innate immune defense against viral infections. Interferon acts as an antiviral in two ways, first, it induces the production of antiviral effector proteins so as to inhibit viral replication in cells and can protect normal cells from viral invasion; second, it activates cellular immunity by activating the proliferation and activation of cytotoxic T lymphocytes, activating natural killer cells (NK) and macrophages to eliminate viruses. Lack of endogenous interferon in the body can cause reduced activity as an antiviral. Children are susceptible to viral infections due to immature immune function and relatively low levels of humoral and cellular immunity and secretion of interferons (Shen & Yang, 2020). ACE2 expression and affinity increase with age. Therefore, in the nasal epithelium of the upper respiratory tract of children, lower expression of ACE2 may assist in reducing the transmission of SARS-CoV-2 infection (Patel & Verma, 2020).

Interferon-α can reduce the viral growth spurt in the early stages of infection, thereby reducing symptoms and shortening the course of the disease. Interferon-α is used in bronchiolitis, viral pneumonia, acute upper respiratory tract infections, oral diseases, SARS, and other viral infections in children. Interferon-α nebulization at a dose of 200,000–400,000 IU/kg or 2-4 μg/kg in 2 mL of sterile water, nebulize twice a day for 5-7 days is the recommended use. In addition, the interferon-α2b spray is used in high-risk populations with close contact with patients suspected of being infected with COVID-19 or patients who are in the early phase who only have symptoms in the upper respiratory tract. The nebulizer was used during treatment by giving patients a dose of 8000 IU interferon-α2b per injection once every 1-2 hours and 8-10 sprays/day for 5-7 days on each side of the nasal cavity and 8-10 sprays on the oropharynx. (Shen *et al.*, 2020).

Supportive care such as fluids, adequate calories, and oxygen supplementation should be used in the care of children infected with human coronaviruses (HCoVs) to prevent acute respiratory distress syndrome, organ failure, and secondary nosocomial infections. If the

patient is suspected of having a bacterial infection, broad-spectrum antibiotics such as second or third generation cephalosporins can be given (Zimmermann & Curtis[1], 2020).

4.3 Effectivity of interferon

Critical management of COVID-19 is largely a supportive therapy by giving low-dose corticosteroids, lopinavir/ritonavir, and interferon inhalation atomization to decreased mortality rate (Liu *et al.*, 2020). A multicenter, randomized, double-blind, placebo-controlled trial with a total of 163 patients at least 14 years old were included in the complete analysis set (FAS) and 151 patients were included in the per-protocol set (PPS). There were patients in the IFNα1b group and patients in the control group. The control group showed that recombinant human interferon α1b (IFNα1b) aerosol is safe and reduces clinical symptoms of non-influenza viral pneumonia (Jiang *et al.*, 2020). Therefore, interferon can be used in the critical handling of COVID-19 by reducing clinical symptoms.

Interferon α1b therapy in 75 pediatric COVID-19 patients obtained a 100% cure rate. Most children recover within two weeks. This is due to the less severity of children than adults (Peng *et al.*, 2020). During the SARS outbreak in 2003, an animal study revealed that human recombinant interferon-α2b inhalation could prevent SARS-CoV infection in a Rhesus monkey model by inhibiting infection and viral replication. Population studies further reveal that human recombinant interferon-α2b inhalation can effectively reduce the infection rates of respiratory viruses, influenza viruses, adenoviruses, and SARS-CoV (Shen & Yang, 2020).

Interferon-β1 is a safe and easy treatment against COVID-19 in the early stages of infection. Similar treatments have mixed efficiency against the MERS-CoV and SARS-CoV viruses, but *in vitro* studies have shown that SARS-CoV-2 is substantially more sensitive to interferon-I than other coronaviruses. Research on animal interferon-I treatment for COVID-19 is lacking but its safety has been assessed in various independent clinical trials (Sallard *et al.*, 2020). Investigator-initiated, open-label, single-arm clinical trial research in 20 adult patients with suspected COVID-19 supports the use of interferon beta-1a as an adjunct to the antiviral treatment recommended in COVID-19 patients. However, a parallel two-armed randomized clinical trial is needed to ensure its efficacy and safety (Payandemehr *et al.*, 2020). As described above, only one study was conducted in children, and the others were over 14 years of age and adults therefore it is necessary to conduct studies in a larger sample of pediatric patients.

Interferon is also used in Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Comparison of the efficacy of remdesivir and the combination of lopinavir/ritonavir and interferon-β against MERS-CoV showed that remdesivir and interferon-β had better antiviral activity than lopinavir/ritonavir *in vitro*. Lopinavir/ritonavir prophylaxis plus interferon-β slightly reduces viral load without affecting other disease parameters and improves lung function but does not reduce viral replication or severe pulmonary pathology (Sheahan *et al*, 2020). Interferon-α and interferon-β have *in vitro* activity against SARS-CoV and MERS-CoV. Interferon-β showed the strongest in vitro inhibition against MERS-CoV with the lowest IC_{50} of 1.3 U/mL compared to other subtypes. The efficacy of antiviral combinations and various interferon subtypes such as PegIFN-α2b, IFN-α1b, IFN-β1a is still being studied in COVID-19 patients (ChiCTR2000029387, NCT04293887, NCT04254874) (Tidwong *et al.*, 2020).

Interferon products such as Pegasys® (PEGylated interferon alpha-2a) and PegIntron® (PEGylated interferon alpha-2b) induce an innate antiviral immune response against Hepatitis B and C. Pegasys® products are subject to pharmacokinetic studies in children aged 2-8 years with Hepatitis. C chronic. The results showed 4-fold lower clearances and take longer time to reach the steady-state (12 weeks compared to 5-8 weeks), and 25-70% higher of its AUC in children compared to adults. A study in children with the PegIntron® product evaluated pediatric patients aged 3-17 years and showed about a 50% increase in AUC compared to adults with the equivalent dose. Both nano-formulations showed increased total bioavailability and reduced clearance compared to non-PEGylated preparations (Yellepeddi *et al.*, 2019).

In PEGinterferon alpha-2b there is a urethane bond that is connected to PEG with interferon so that PEGinterferon alpha-2b is unstable and easy to hydrolyze and after being injected the original alpha-2b interferon circulates in the body. PEGinterferon alfa-2b can be considered a prodrug of interferon alpha-2b. Whereas in PEGinterferon alpha-2a, there is an amide chain connected to the PEG chain with interferon-alfa-2a which does not undergo hydrolysis. Despite these differences, the efficacy, safety, and tolerability of the two peginterferons are very similar (Noureddin & Ghany, 2010).

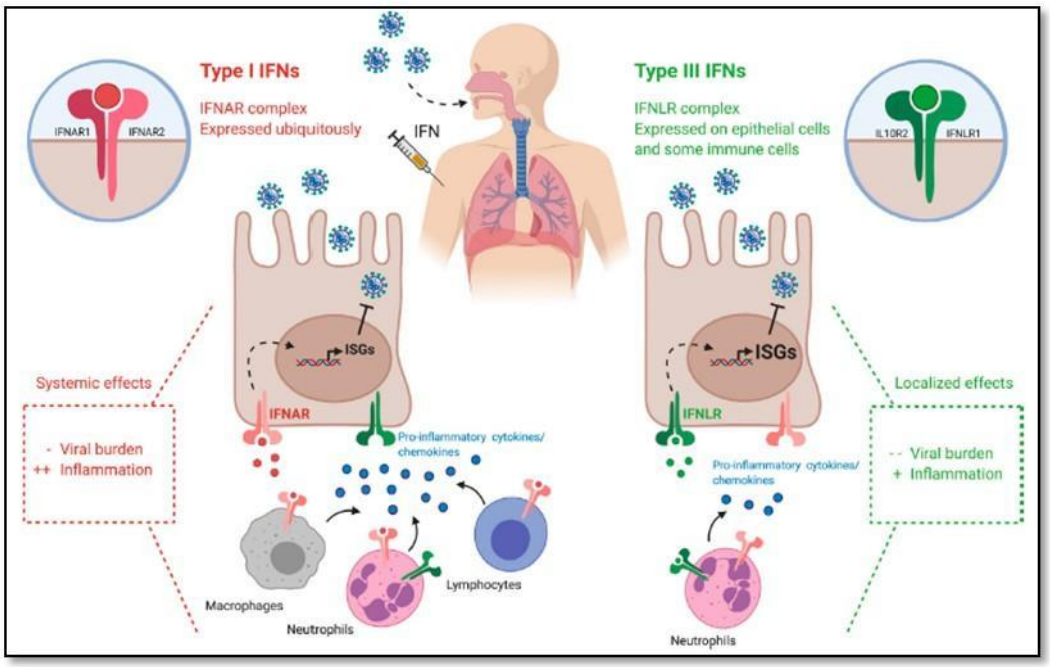

Figure 2. Potential mechanisms for using interferon as a preventive therapy and treatment of COVID-19. (Prokunina-Olsson *et al.*, 2020)

The potential mechanism for using interferon therapy is shown in Figure 2. IFN type I (IFN-α / β) signals through a heterodimeric receptor complex, namely IFNAR which consists of IFNAR1 and IFNAR2 subunits. IFNAR activation induces gene expression and triggers a pro-inflammatory response. IFNAR is expressed on all cells which can cause serious systemic side effects. In contrast, the IFN type III signal (IFN-λ1-4) passes through a different receptor complex, namely IFNLR which consists of IL10R2 and IFNLR1 subunits. IFNLR1 expression is limited to epithelial cells and immune cell subsets, including neutrophils. Therefore, giving IFN type III as a prophylactic treatment or in the early stages of COVID-19 will induce gene expression and antiviral response only in epithelial cells, thereby reducing side effects and inflammation (Prokunina-Olsson *et al.*, 2020). Interferon type I can improve respiratory disorders, relieve lung disorders, establish better saturation, and reduce the need for additional oxygen. Interferon type I was well tolerated and did not increase any adverse effects. Interferon type I is therefore recommended as a first-line antiviral for SARS-CoV-2 infection in a local protocol, with timely administration and monitoring of side effects. A well-designed large-scale prospective randomized control trial is needed to provide stronger evidence on this topic (Yu *et al.*, 2020). Interferon is safe and comfortable to enhance treatment in the early stages of COVID-19 infection and can protect the respiratory tract. Interferon was combined with

Lopinavir/Ritonavir, and Hydroxychloroquine, and Remdesivir in the WHO's first clinical trial (Sujaritha *et al.*, 2020).

4.4 Adverse events of interferon

Adverse events of interferon-α include flu-like syndromes namely headache, fever, chills, myalgia, and malaise which usually occur within 6 hours of dosing. This flu syndrome occurs in more than 30% of patients during the first week of therapy and tends to recover after continued administration. Temporary liver enzyme elevations may occur in the first 8-12 weeks of therapy. Potential side effects during chronic therapy include neurotoxicity such as mood disorders, depression, drowsiness, confusion, and seizures. High doses of Interferon-α intramuscular injection of more than 2 μg/kg/time can cause myelosuppression in children. Additionally, it can cause weight loss, rash, cough, myalgia, alopecia, tinnitus, reversible hearing loss, retinopathy, pneumonitis, and possibly cardiotoxicity. Autoantibody induction can occur which causes exacerbations (Wang & Zhu, 2020).

Contraindications of interferon-α include liver decompensation, autoimmune disease, and a history of cardiac arrhythmias. Caution is advised in psychiatric illness, epilepsy, thyroid disease, ischemic heart disease, and cytopenia. Interferon-α should not be given to children with creatinine (CrCl) below 50 mL/minute. Interferon-α nebulization should be used with caution in neonates and infants under 2 months of age. Suicidal ideation is more common in children, especially adolescents compared to adults (2.4% vs 1%) (Wang & Zhu, 2020). The combination of Interferon-α and Ribavirin can inhibit growth and development in children. Potential drug-drug interactions include elevated levels of theophylline and methadone. Co-administration with didanosine is not recommended because it has a risk of liver failure, and co-administration with zidovudine can worsen cytopenia. Interferon-α should be used with caution when combined with sleeping pills and sedatives.

The only adverse event in the Cohort study were mild flu-like symptoms such as low-grade pyrexia, rhinorrhea, and neutropenia, which were transient in some children in the early stages of treatment. There is no reduction in dosage or discontinuation of treatment in children with flu-like symptoms, and neutropenia disappears rapidly. There were no patients with hypothyroidism/hyperthyroidism side effects or dose modification required for thyroid dysfunction. No severe abnormal results were observed in other laboratory data. The sample

size in this study is small and the sample size needs to be expanded in future studies. In addition, in monitoring for side effects, growth parameters were not measured or recorded completely to monitor the impact of antiviral treatment on children's growth and development (Hu *et al.*, 2019).

5. Conclusions

Interferon is a safe treatment for children with COVID-19 because it can reduce clinical symptoms and decrease the mortality rates. The use of interferon in COVID-19 in children has a high cure rate because the severity of COVID-19 in children's cases is lower than in adults. However, the results of interferon therapy in COVID-19 need to be evaluated in a larger sample of pediatric patients.

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