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INTERFERON NEBULATION IN COVID-19 PATIENTS

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ABSTRACT

This study aims to see how effective interferon nebulization therapy is in COVID-19 patients. The method used is rapid review. The results of the study showed that rSIFN-co therapy has advantages, namely the duration of faster clinical improvement, the time for negative conversion of viral nucleic acid on mechanical ventilation is also shorter. While interferon-alpha therapy itself, because it still uses traditional principles, clinical improvement that occurs is a little slow. Conclusion, the use of interferon-alpha is less effective for the treatment of COVID-19 than the use of rSIFN-co therapy.

Keywords: COVID-19, Interferon, Nebulization

INTRODUCTION

Coronavirus is a type of virus that can infect the respiratory tract with the initial target being the epithelial cells lining the alveoli and mucosa in the respiratory tract. Presentation of the viral antigen stimulates the humoral and cellular immune response to fight the virus (Sharma et al., 2021). An inadequate or excessive immune response can cause tissue damage, causing respiratory tract disorders (Samuel, 2023). Shortness of breath or dyspnea is the most common sign and symptom in COVID-19 positive patients. Shortness of breath occurs because the lungs are not supplied with oxygen, causing shallow and rapid breathing (Tali et al., 2021). Therefore, nebulization therapy is carried out to relieve the symptoms of shortness of breath experienced by patients (Zhou et al., 2020).

In December 2019, the first case of a mysterious pneumonia was reported in Wuhan, Hubei Province. The source of transmission of this case is still unknown, but the first case was linked to a fish market in Wuhan. From December 18 to December 29, 2019, there were five patients treated with Acute Respiratory Distress Syndrome (ARDS) (Ochani et al., 2021). From December 31, 2019, to January 3, 2020, this case increased rapidly, marked by the report of 44 cases. In less than a month, this disease has spread to various other provinces in China, Thailand, Japan, and South Korea. The samples studied showed a new coronavirus etiology. Initially, this disease was temporarily named 2019 novel coronavirus (2019-nCoV), then WHO announced a new name on February 11, 2020, namely Coronavirus Disease (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) virus (Nugraha et al., 2020). This virus can be transmitted from human to human and has spread widely in China and more than 190 other countries and territories on March 12, 2020, WHO declared COVID-19 a pandemic. As of March 29, 2020, there were 634,835 cases and 33,106 deaths worldwide. Meanwhile, in Indonesia, 1,528 positive cases of COVID-19 and 136 deaths have been determined (Susilo et al., 2020).

Nebulization is the most common and easy technique to deliver large volumes of liposomes in droplet form to the lungs (Hasselbalch et al., 2020; Pan et al., 2023). There is no coordination required between inhalation and actuation making nebulizer delivery devices

suitable for unconscious patients, patients with severely compromised lungs, the elderly, and pediatrics. There have been several studies that have conducted interferon nebulization therapy in COVID-19 patients (Eisen et al., 2021). The interferon (IFN) family of proteins plays a key role in the immune response to viruses and other pathogens (Lim et al., 2023). Interferons are a family of cytokines with antiviral properties in vitro and in vivo. In the context of COVID-19, IFN has been shown to be key to containing SARS-CoV-2 infection but has also been described as a trigger for severe symptom (Jiang et al., 2022).

In particular, previous studies have demonstrated the in vitro activity of IFN against SARS-CoV and Middle East respiratory syndrome coronavirus (Primorac et al., 2022). Recently, several randomized controlled trials (RCTs) have been conducted to assess the clinical efficacy and safety of IFN-β alone or with other antiviral agents in the treatment of COVID-19 patients (Chen et al., 2022). However, the results obtained from previous studies are inconsistent and it is not fully understood how each member of the IFN family contributes to various aspects of COVID-19. Therefore, this study aims to clarify the effects and effectiveness of interferon nebulization therapy in COVID-19 patients through a literature review, which in previous studies showed inconsistent results.

RESEARCH METHOD

In its preparation, this literature review uses a rapid review method regarding the effectiveness of the use of interferon nebulization therapy in COVID-19 patients. The article search process begins with determining keywords using the PICO framework. In this literature review, the element P (population) refers to COVID-19 patients, I (intervention) refers to interferon nebulization, and O (outcomes) refers to respiratory status. Then all the keywords used are arranged into one search sentence, namely "COVID-19 patients AND interferon nebulization AND respiratory status". Furthermore, based on the search sentence that has been compiled, an article search was carried out from three databases, namely Scopus, PubMed, and CINAHL.

The inclusion criteria used in the article search are articles that can be accessed free-full text, in English, published in the last 5 years (2019-2024), using RCT, quasi-experimental, or analytical study designs, and the population and samples used are COVID-19 patients, and the intervention is focused on discussing the use of interferon nebulization. Meanwhile, the exclusion criteria used are if the article has an output that is not focused on discussing the effectiveness of the use of interferon nebulization or the population and samples used are patients with conditions other than COVID-19. After systematically searching and selecting articles using the 2020 prism diagram, 3 articles were obtained that were worthy of being reviewed because they met the topic criteria specified in this literature review.

RESULT

Table. 1
Review Results

Author's Name, Article Title, Research Method	Research Objectives	Findings
Li et al., (2021) Effect of a genetically engineered interferon-	To compare the efficacy of a novel	A total of 102 COVID-19 patients from five hospitals in China were recruited and assessed for eligibility by receiving rSIFN-co

alpha versus traditional interferon-alpha in the treatment of moderate-to-severe COVID-19: a randomised clinical trial Multicenter randomized (1:1) trial	genetically engineered recombinant interferon super-compound (rSIFN-co) with traditional interferon-alpha added to initial antiviral agents (lopinavir-ritonavir or umifenovir) for the treatment of moderate to severe COVID-19.	nebulization or interferon-alpha nebulization added to baseline antiviral agents for no more than 28 days. Of the 102 patients finally, only 46 patients were assigned to the rSIFN-co group and 48 patients were assigned to the interferon-alpha group for evaluation. The overall clinical improvement rate at day 28 was significantly higher in the rSIFN-co group than in the interferon-alpha group. The time to radiological improvement in the rSIFN-co group was significantly shorter than that in the interferon-alpha group. The time to negative conversion of viral nucleic acid on mechanical ventilation applied to these patients in the rSIFN-co group was also significantly shorter than that in the interferon-alpha group. rSIFN-co may be a potential and more efficient therapy than traditional interferon-alpha in conducting this exploratory, head-to-head trial.
Monk et al., (2021) Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial RCT	Evaluate the potential effects of inhaled interferon beta1-a formulation (SNG001) in hospitalized patients with confirmed SARS-CoV-2 infection.	The odds of improvement on the OSCI scale were more than twofold greater in the SNG001 group than in the placebo group at day 15 or 16. Three patients died during the study; all deaths occurred in patients in the placebo group, 11 (22%) patients in the placebo group developed severe disease or died (OSCI 5) between the first dose and day 16 compared with six (13%) patients in SNG001. Compared with six, SNG001 reduced the odds of developing severe disease or death by 79%. Over the 14-day treatment period, patients in the SNG001 group were more than twice as likely to recover compared with the placebo group. namely (21 [44%] of 48 with SNG001 and 11 [22%] of 49 with placebo. A total of 26 (54%) patients in the SNG001 group and 30 (60%) in the placebo group had treatment-emergent adverse events. Adverse events: Fewer patients experienced serious adverse events in the SNG001 group compared with the placebo group (seven [15%] vs 14 [28%]). The most common serious adverse events were related to COVID-19: respiratory failure (three [6%] patients in the SNG001 group vs six [12%] in the placebo group) and pneumonia (three [6%] vs three [6%]). Other treatment-emergent adverse events related to SNG001, each occurring in one patient, included decreased oxygen saturation, diarrhea, dry throat, mouth pain, night sweats, and tremor. m placebo group: nausea, multiple organ dysfunction syndrome (fatal), and pulmonary embolism (fatal). In addition to the fatal

		treatment-related side effects described above, a third patient in the placebo group died, with the cause of death listed as COVID-19 pneumonia.
Zhou et al., (2020) Interferon-α2b Treatment for COVID-19 RCT	Describes the effects of treatment with interferon (IFN)-α2b in a cohort of confirmed COVID-19 cases in Wuhan, China.	Clinical and Laboratory Data: Moderate COVID-19 Disease 77 adults with confirmed COVID-19 were admitted to Union Hospital, Wuhan, and at the discretion of the admitting physician, were treated with nebulized IFN-α2b (n = 7), ARB (n = 24) or combination therapy of IFNÿ2b plus ARB (n = 46). All patients received a variety of prophylactic antibiotics, so there were no cases of proven or suspected bacterial infection. Effect of IFN Treatment on Viral Clearance Specifically, analysis of the results suggested that treatment with IFN-α2b, either alone or in combination with ARB, accelerated viral clearance when compared with ARB treatment alone. The median days to viral clearance were 27.9 for patients treated with ARB alone, 21.1 days for those treated with IFN alone and 20.3 days for those treated with IFN + ARB (from symptom onset). Data showed a statistically significant acceleration of viral clearance from the upper respiratory tract in patients receiving IFN-α2b treatment (20.4 days, p = 0.002), i.e., IFN treatment accelerated viral clearance by 7 days. Effect of IFN Treatment on Circulating Cytokine Levels and Inflammatory Biomarkers While circulating IL-6 levels remained low for all patients receiving IFN, those receiving ARB alone (i.e., without IFN) showed a significant spike in circulating IL-6 levels. Specifically, during the time period from day 12 to day 42 (from symptom onset), patients in the ARB alone group had higher IL-6 levels on average than patients treated with IFN alone or the combination of IFN + ARB, by 33.5 pg/mL.

rSIFN-co was associated with a shorter time to clinical improvement than traditional interferon-alpha in the treatment of moderate to severe COVID-19 when combined with basic antiviral agents. rSIFN-co therapy alone or in combination with other antivirals is worthy of further study. After a comparison was made between the rSIFN-co group and the interferon-alpha group. From various test results, it is known that rSIFN-co may be a potential therapy and more efficient than traditional interferon-alpha for the treatment of moderate to severe COVID-19. Therefore, rSIFN-co therapy or combined with other antivirals is worthy of further study related to its effectiveness and mechanism.

Treatment with interferon beta1-a with the SNG001 formulation is a treatment that has been researched, studied and proven to be well tolerated in patients with asthma and COPD, and it also appears to be well tolerated in Covid-19 patients. SNG 001 fluid has been shown to accelerate recovery and has minimal serious side effects. Unlike the placebo formula which has fatal side effects and causes death, it is less recommended as a treatment for the Covid-19 virus. Patients receiving inhaled interferon beta1-a treatment with the SNG001 formulation had a greater chance of recovering from COVID-19 infection than those given placebo, which could strengthen the case for a larger international study to further investigate the effectiveness of the SNG001 formulation against COVID-19.

Treatment with IFN-α2b with or without arbidol significantly reduced the duration of detectable virus in the upper respiratory tract and in parallel reduced the duration of elevated blood levels of the inflammatory markers IL-6 and CRP. Analysis showed that inhaled IFN-α2b accelerated viral clearance from the respiratory tract and accelerated resolution of the systemic inflammatory process when compared with ARB treatment alone. Therapeutic intervention of IFN-α2b administration in COVID-19 patients is recommended as an antiviral intervention. Beyond the clinical benefits for individual patients, treatment with IFN-α2b may also be beneficial for public health measures aimed at slowing the wave of this pandemic, where the duration of viral shedding appears to be shortened. Therefore, IFN-α2b should be further investigated as a therapy in COVID-19 cases.

DISCUSSIONS

In the first article, which discusses the effectiveness of the novel genetically engineered recombinant super-compound interferon (rSIFN-co) with traditional interferon-alpha by comparing the effectiveness of both. This study was conducted as a multicenter, head-to-head, randomized, single-blind clinical trial by recruiting patients from five hospitals in Wuhan. A total of 102 COVID-19 patients from five hospitals in China were recruited and assessed for eligibility by receiving rSIFN-co nebulization or interferon-alpha nebulization added to basic antiviral agents for no more than 28 days. The results obtained after the study were that the use of interferon-alpha was less effective for the treatment of COVID-19 than the use of rSIFN-co therapy. In the study, there were 102 patients who were sampled with a ratio of 46 patients included in the rSIFN-co group and 48 patients included in the interferon-alpha group. At the time of evaluation, the rSIFN-co group was more significant in accelerating the healing or clinical improvement of COVID-19 obtained on day 28 with this head-to-head trial. The advantages of rSIFN-co therapy compared to interferon-alpha therapy are the duration of its faster clinical improvement, the time for negative conversion of viral nucleic acid on mechanical ventilation is also shorter. While interferon-alpha therapy itself, because it still uses traditional principles, the clinical improvement that occurs is a little slow (Li et al., 2021).

However, this is not in accordance with research conducted by Sosa et al., (2021) which states that shows encouraging data on IFN-β 1b effectiveness against the novel COVID-19 infection. When added to the current standard of care, IFN-β has been shown to decrease the overall hospitalization stay and decrease the severity of COVID-19 respiratory symptoms. Some studies have reduced ICU stay, enhanced the survival rate, and decreased invasive mechanical ventilation needs in severe cases compared to control. Adverse effects in COVID-19 patients receiving IFN-β included neuropsychiatric symptoms, diarrhea, fever, nausea, and mild ALT elevations.

A retrospective cohort study showed that early use of interferon-alpha-2b could reduce in-hospital mortality and early initiation of interferon with lopinavir-ritonavir was associated with better clinical response than lopinavir-ritonavir alone in COVID-19 patients (Wang et al.,

2020). Another exploratory study showed that interferon-alpha-2b therapy appeared to shorten the duration of viral shedding and reduce inflammatory markers interleukin-6 and C-reactive protein, supporting the potential of interferon-alpha-2b as a therapy for COVID-19 (Zhou et al., 2020). The study conducted by Li et al., (2021) is the first RCT to show that the combination of rSIFN-co and antiviral agents can achieve encouraging results, even in moderate to severe cases. Meanwhile, this study confirmed the superiority of rSIFN-co compared with interferon-alpha when used in combination with basic antiviral agents. The overall clinical improvement rates were 93.5% and 77.1% on day 28 in the rSIFN-co and interferon-alpha groups, respectively. Based on the fact that basic antiviral agents (lopinavir-ritonavir or umifenovir) may be ineffective in treating COVID-19 when used alone (Cao et al., 2020), we suggest that the antiviral effect is mainly attributed to interferon-alpha or the synergy of the combination. These findings suggest that the combination of interferon with antiviral agents is a potential therapeutic approach for COVID-19. rSIFN-co plus lopinavir-ritonavir or umifenovir may be an effective therapy for treating COVID-19. Recently, remdesivir was shown to be superior to placebo in shortening the time to recovery in adults hospitalized with COVID-19 (Beigel et al., 2020). The combination of rSIFN-co and remdesivir is highly anticipated in the future.

In the second article, SNG001 (6 MIU of interferon beta-1a) or placebo was administered via an I-neb nebulizer (Philips Respironics, Murrysvile, PA, USA) once daily for 14 days. During the 14-day treatment period and while patients were in the hospital, vital signs and level of consciousness or evidence of confusion or agitation, or both, were recorded twice daily. In addition, assessment for pneumonia by chest auscultation (and other forms of physical examination if deemed necessary), OSCI, BCSS was performed daily. OSCI assessment, blood sampling, and 12-lead ECG assessment, as well as chest radiography if required, were performed 24 hours after the patient's last dose. Patients were also regularly assessed for signs or symptoms that might be considered adverse effects related to the study drug (Monk et al., 2021).

The results of this trial showed that the odds of improvement on the OSCI scale were more than twofold greater in the SNG001 group compared with the placebo group at day 15 or 16. Three patients died during the study; all deaths occurred in patients in the placebo group. Eleven patients (22%) in the placebo group had worsening disease or death (OSCI 5) between the first dose and day 16. In contrast, six patients (13%) in the SNG001 group showed a 79% reduction in the odds of developing severe disease or dying. Over the 14-day treatment period, patients in the SNG001 group were more than twice as likely to recover (21 of 48 SNG001 patients and 11 of 49 placebo patients). However, 26 patients (54%) in the SNG001 group and 30 patients (60%) in the placebo group had treatment-emergent adverse events. Research conducted by Sosa et al., (2021) conveys adverse events in COVID-19 patients receiving IFN-β included neuropsychiatric symptoms, diarrhea, fever, nausea, and mild ALT elevations. One case of hypersensitivity was also noted.

In the third article, an uncontrolled exploratory study was conducted in 77 hospitalized adults with confirmed COVID-19 treated with nebulized IFN-α2b (5 mU bid), arbidol (200 mg tid) or the combination of IFN-α2b plus arbidol. Serial SARS CoV-2 testing along with hematologic measurements, including cell count, blood biochemistry and serum cytokine levels, as well as temperature and blood oxygen saturation levels, were recorded for each patient throughout their hospital stay. Clinical and laboratory data, 77 adults with COVID-19 were treated with nebulized IFN-α2b (n = 7), ARBs (n = 24) or the combination of IFNo2b plus ARBs (n = 46) at the discretion of the admitting physician. All patients also received antibiotics to prevent bacterial infection (Zhou et al., 2020).

Analysis of the results suggested that treatment with IFN-α2b, either alone or in combination with ARB, accelerated viral clearance. The median days to viral clearance were 27.9 for patients treated with ARB alone, 21.1 days for those treated with IFN alone and 20.3 days for those treated with IFN + ARB (from symptom onset). There was a statistically significant acceleration in viral clearance from the upper respiratory tract in patients treated with IFN-α2b (20.4 days, p = 0.002), i.e., IFN treatment accelerated viral clearance by 7 days. Effect on circulating levels, Circulating IL-6 levels remained low for all patients receiving IFN, those receiving ARB alone (i.e., without IFN) showed a significant spike in circulating IL-6 levels. On average, patients in the ARB alone group had higher IL-6 levels than patients treated with IFN alone or the IFN + ARB combination, by 33.5 pg/mL. Research conducted by Chen et al., (2022) states thatadding INF-β to treatment regimens did not significantly improve the clinical outcomes of hospitalized patients with COVID-19. Adding INF-β could not reduce the requirements of MV or ECMO for respiratory support, could not significantly increase the rate of survival to hospital discharge, and could not shorten the time to clinical improvement and length of hospital stay in patients with COVID-19.

CONCLUSION

Based on the third article that has been reviewed, this review discusses the treatment of COVID-19 by administering drugs (rSIFN-co) with traditional interferon-alpha added to the initial antiviral agent (lopinavir-ritonavir or umifenovir), inhaled interferon beta1-a with formulation (SNG001), and interferon (IFN) -α2b. This article states that the use of interferon-alpha is less effective for the treatment of COVID-19 compared to the use of rSIFN-co therapy. rSIFN-co therapy has the advantage of a faster duration of clinical improvement, the time of negative conversion of viral nucleic acid on mechanical ventilation is also shorter. While interferon-alpha therapy itself, because it still uses traditional principles, the clinical improvement that occurs is slightly slow. In addition, there is also the SNG001 drug which is given once a day for 14 days.

SUGGESTION

Giving this drug more than doubles the possibility of recovery, but in this treatment there are side effects that appear. The use of IFN-α2b treatment, either alone or in combination with ARB, accelerated viral clearance and IFN treatment accelerated viral clearance by up to 7 days. Therefore, the use of interferon nebulization therapy is not recommended for COVID-19 patients and it is hoped that further randomized clinical trials with large sample sizes can be carried out to properly assess the efficacy of interferon therapy in COVID-19 patients.

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