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LETTER TO EDITOR

Interferon-α-2b Nasal Spray for Treating SARS-CoV-2 Omicron Variant-Infected Children

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To the Editor,

SARS-CoV-2 Omicron variant-infected pediatric patients tend to be younger, and the symptoms turn milder. Infected young children, not eligible for vaccination and novel antiviral therapies, shed the virus longer, and are more likely to transmit SARS-CoV-2 infection than adults. Shortening viral shedding time in children is key for curbing virus transmission. Inhaled IFN α-2b therapy was reported to reduce the SARS-CoV-2 viral shedding in adults without serious adverse effects [1–3]. In addition, Omicron variants replicate mostly in the upper airway. We hypothesize that IFN α-2b nasal spray (nIFN), a convenient and feasible focal antiviral therapy, is effective in shortening viral shedding in children.

This is a phase II, open, randomized, single-center, and controlled study (Clinical Trial: NCT05381363) to evaluate the efficacy of nIFN (Tianjin Sinobioway Biomedicine, 2 million IU/ml = 240 sprays) in SARS-CoV-2 Omicron-infected children aged 1 to 14. From 1st May to 30th May 2022, eligible symptomatic patients admitted to Renji Hospital (South branch), a dedicated hospital for treating COVID-19 children in Shanghai, were randomly allocated into two groups: the nIFN + standard of care treatment (SC) intervention group and the SC control group. The 3-day nIFN treatment was initiated within 5 days of the onset of symptoms. The primary outcome was viral shedding time ($VST^{Ct>35}$) defined as the time duration from the symptom onset to the first PCR cycle threshold (Ct value) > 35. The secondary outcomes included $VST^{Ct>30}$, $VST^{Ct>33.5}$, and adverse effects. The trial groups with a two-sided significance level of 5%. The hazard ratio and 95% confidence intervals were calculated for VSTs. Survival analyses were performed by log-rank test. The details of this study, such as patient enrollment, nIFN intervention (Table S1), and standard treatment were demonstrated in the supplementary methods.

A total of 268 children were recruited (Fig. S1). Children's characteristics were similar in the intervention ($n = 126$) and control groups ($n = 142$) (Table S2). The primary outcome, viral shedding time, showed a significant difference between groups ($VST^{Ct>35}$, 10.9 ± 3.0 vs 11.6 ± 3.3, $P = 0.048$). Secondary outcomes, including $VST^{Ct>33.5}$ and $VST^{Ct>30}$, were both significantly shorter in the nIFN + SC group than those in the SC group.

Subgroup analyses demonstrated that nIFN was mainly effective for shortening $VST^{Ct>35}$ in unvaccinated children as well as children aged 12 to 24 months old, and also effective in shortening $VST^{Ct>33.5}$ and $VST^{Ct>30}$ of children with mild COVID-19 infection, children yet to be vaccinated, and children aged 12 to 48 months old. See Fig. 1 There were no serious adverse events observed in the nIFN + SC group, all children in the intervention group completed the 3-day nIFN therapy and no patients in either group progressed to a severe form of COVID-19 or died.

This study found that nIFN could shorten the SARS-CoV-2 viral shedding time, especially in unvaccinated and young children (12–24 months). Vaccination is the first choice to protect against infection in healthy children. For already infected cases, when most of the anti-viral medications were not approved for young children, nIFN may provide benefits. Because once infected with SARS-CoV-2, it takes a longer time for virus clearance in young children and is a potential transmission source for household infection.

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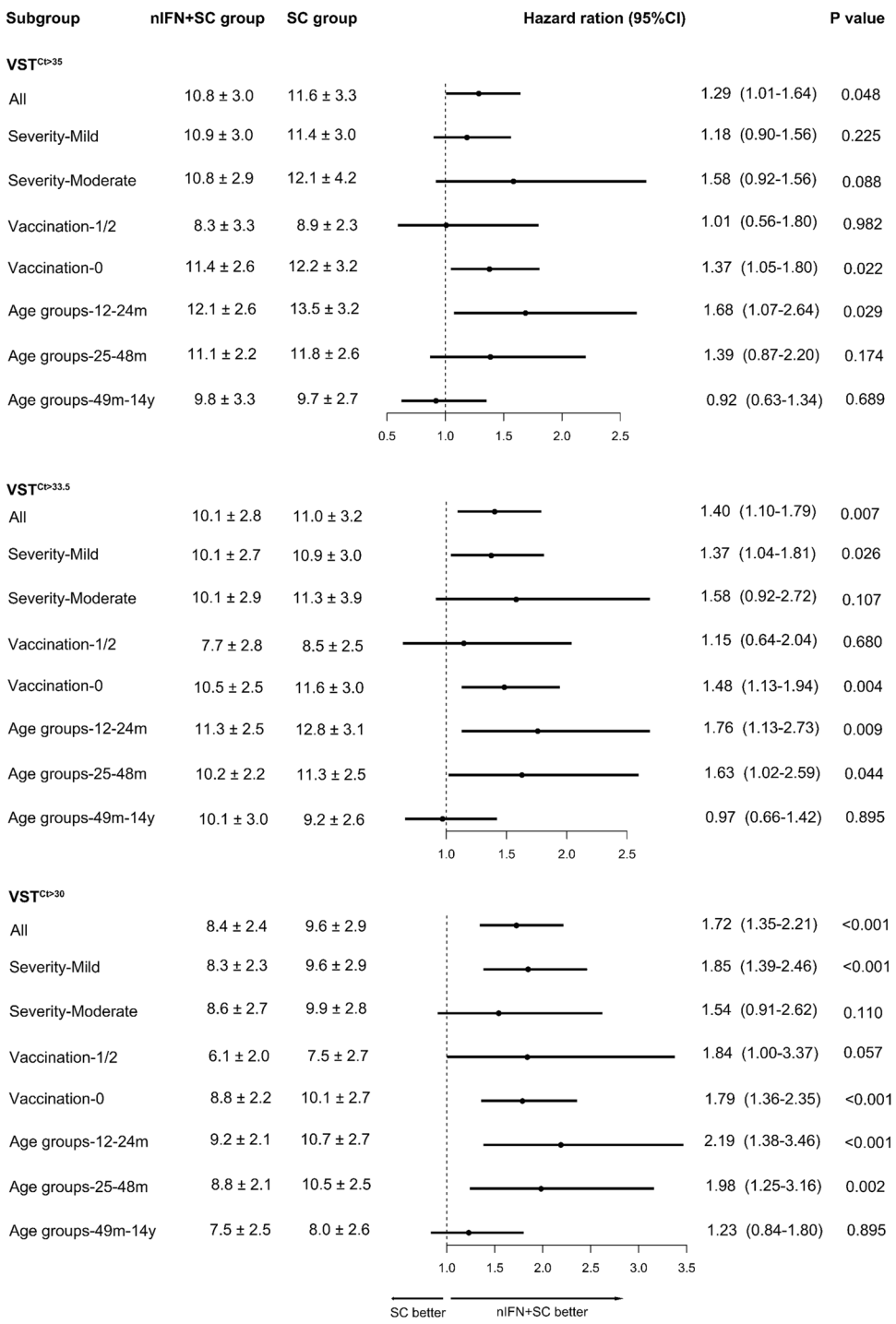

Fig. 1 Subgroup analyses for the different endpoints. Subgroup analyses of the different viral shedding times were conducted. Hazard ratio analyses and 95% confidence intervals were provided to evaluate whether the treatment effect varied according to age, severity, and vaccination. (nIFN, interferon-α-2b nasal spray; SC, standard care; $VST^{Ct>35}$, viral shedding time defined as the time duration from the symptom onset to the first PCR cycle threshold (Ct value) > 35; $VST^{Ct>33.5}$, time from the symptom onset to the first Ct value > 33.5; $VST.^{Ct>30}$, time from the symptom onset to the first Ct value > 30)

The mechanisms of the efficacy of nIFN in treating virus infection have been well studied. It was reported to reduce the circulating levels of the inflammatory biomarkers IL-6 and C-reactive protein and improve lung disease [4]; however, systematic absorption of nIFN has not been reported. According to the results presented in this study, the nIFN is a convenient and effective medication without serious adverse effects for children with mild to moderate COVID-19. The reported side effects include transient fever, digestive upsets, fatigue, weight loss, reduced white blood cell count, elevated transaminases, and so on. No severe side effects were reported.

RT-qPCR tests provide semiquantitative results in the form of Ct values, which are inversely correlated with viral loads and are useful in determining the need for isolation and quarantine [5]. When a Ct value of 33.5 or 30 was used

as proxies of negative viral shedding in most countries and regions, nIFN could be more effective in shortening the isolation time according to the results of our secondary outcomes. In this study, the 3-day nIFN was initiated within the first 5 days of the symptom onset. Whether pediatric patients could benefit from a longer treatment warrants further studies.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10875-023-01452-4.

Author Contribution HY and LW conceived, designed, and supervised the study. JZ and XC drafted the manuscript. XC conducted the data analysis and prepared the tables and figures. YL contributed to the manuscript revision and result interpretation. All of the authors confirm the originality of the content.

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Data Availability The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest The authors declare no competing interests.

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