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Inhaled interferons beta and SARS-COV2 infection: a preliminary therapeutic perspective

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ABSTRACT

Introduction: SARS-COV2 infection represents a therapeutic challenge due to the limited number of effective therapies available and due to the fact that it is not clear which host response in terms of inflammation pattern is the most predictive for an optimal (and rapid) recovery. Interferon β pathway is impaired in SARS-COV2 infection and this is associated with a bigger disease burden. Exogenous inhaled interferon might be beneficial in this setting.

Areas covered: Nebulized interferon-β is currently investigated as a potential therapy for SARS-COV2 because the available data from a phase II study demonstrate that this medication is able to accelerate the recovery from disease.

Expert opinion: Further clinical studies are needed in order to better document the efficacy of this therapy especially in severe forms of COVID-19, the optimal duration of therapy and if such a medication is appropriate for domiciliary use. Also combined regimens with antivirals or with compounds which are able to enhance the endogenous production of interferon might be of promise.

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1. Introduction

SARS-COV2 infection represents a therapeutic challenge due to the limited number of effective therapies available and due to the fact that it is not clear which host response in terms of inflammation pattern is the most predictive for an optimal (and rapid) recovery. Not only Innate immunity is equipped to challenge various viruses including those with respiratory tropism but also these viruses have the means to avoid or even reduce host antiviral pathways. Interferon-beta (IFN-β) is a type I interferon produced at lung level which plays the sentinel role in the antiviral defense. However, it is often 'silenced' by viruses including SARS-COV2, and this results in clinically manifest respiratory tract infections. Inhaled exogenous IFN-β has been evaluated as a therapeutic approach in exacerbated asthma, COPD, and most recently in COVID-19. This short report focuses on the latter aspect discussing the scientific rationale for its use in SARS-COV 2 infection and the available clinical data.

2. SARS-COV2 infection: overview of the inflammatory response

Inflammatory host response in SARS-COV2 infection is initiated upon binding of the angiotensin-converting enzyme 2 (ACE2) which is used to gain intracellular access in lung epithelial cells [1]. With viral migration to the lower respiratory tract, it triggers an innate immune response represented by the activation of the interferon regulatory factors (IRF3 and IRF7) with subsequent production of interferons such as IFN-α and IFN- β (IFN-I type) and INF-γ (IFN-III type) [2]. IFNs are a cytokine family which was described in late 1950s and named after its ability to interfere with viral replication [3]. Type I IFNs are involved in the innate response against viruses or bacteria, whereas type III is more involved in the adaptive immunity [4,5].

In the case of viral respiratory tract infections, besides host's initial antiviral response resulting in the reduction of viral replication and dissemination, IFNs are involved in the initiation of the repair of the bronchial epithelial cells and in the development of the virus specific immunity [6].

SARS-COV2 infection can be associated with a reduced IFN type I response in respiratory tract epithelial cells as well as in the peripheral blood mononuclear cells, this being associated with uncontrolled increase in viral load [7]. This is proven by the results of an experimental study using primary human airway cells experimentally infected with SARS-COV2 virus: it was demonstrated that the apical site of the epithelial (host) cells is essential for virus intracellular infection and subsequent release, in which the presence of virus activates the expression pro-inflammatory cytokines (e.g. TNF-α, IL-6), and most

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Article highlights

- SARS-COV2 infection remains a therapeutic challenge especially in its most severe forms. Lung involvement in SARS-COV2 infection is the most prevalent and the most potentially lethal.
- The existing therapies are not always able to halt the progression of infection and to increase the host defense.
- Interferon pathways are impaired during SARS-COV2 infection and this is associated with increased mortality and prolonged disease course.
- Exogenous inhaled interferon therapy was previously found to be beneficial in the setting of viral exacerbations of asthma and of chronic obstructive pulmonary disease (COPD).
- In SARS-COV2 infection interferon −1a, was evaluated in a phase II clinical trial and found to speed up recovery and to prevent progression to severe disease or death.
- Nebulized interferon −1a also exerted a therapeutic effect on respiratory symptom burden.

importantly that the INF I and III response as a result of virus infection is significantly blunted [8].

The experimental data above mentioned are concordant with the observation that in moderate or severe COVID-19 infection, there is markedly decreased IFN-β endogenous production.

Thus, in a study performed in a cohort of COVID-19 with various stages of the disease, it was demonstrated that the serum INF-β levels were significantly lower compared to that of the healthy individuals [9]. In another study, dynamics of the serum INF-β levels were found to be parallel to that of the COVID-19 disease course, in survivors lower levels at the admission followed by increases during recovery stage being demonstrated [10]. Furthermore, various studies demonstrated that SARS-COV2 proteins such as nsp1, 6, 13, and ORF6 target INF-β in order to evade the host innate immune mechanisms using 'approaches' such as inhibition of INF-β production, inhibition of its downstream signaling and development of resistance to interferon [11,12]. When compounds such as homoharringtonine, narciclasine, and anisomycin which are known to activate the transcription of INF-β were added in vitro to VeroE6 cells infected with SARS-COV2, it was found that they were able to inhibit viral replication thus providing an indirect evidence for the anti-inflammatory role of this type of interferon in COVID-19 [13].

Other types of evidence are represented by the results of two studies demonstrating that inborn errors in the INF-β pathway caused by various gene polymorphisms were associated with an increased risk of severe forms of COVID-19 disease [14,15].

3. Exogenous INF-β in respiratory tract infection due to other viruses

In lower respiratory tract infections due to common viral pathogens such as rhinoviruses, respiratory syncytial viruses or in ARDS, INF-β was also found to be downregulated and this resulted in more severe forms of the disease [16,17].

For example, in an experimental rhinovirus infection induced in COPD patients, it was found that the INF-β response assessed with its quantification in BAL was impaired compared to that of infected healthy subjects, whereas in asthma this was within the normal range if the disease was well (therapeutically) controlled but delayed and suboptimal (in BAL and in serum) in more severe asthma [18,19].

In ARDS, lower IFN-β levels were associated with a more prominent vascular leakage which is one of the main pathogenic features of severity and is associated with a negative outcome for the patient [20].

These findings triggered the investigation of exogenous IFN-β therapy as an antiviral approach in various respiratory tract infections. For example, recombinant human IFN-β was investigated healthy volunteers in whom experimental rhinovirus infection was induced and IFN-β was administered via intranasal route: it was demonstrated that this therapy was associated with lower clinical severity including rhinorrhea and lower nasal rhinovirus excretion [21].

Inhaled recombinant IFN-β was also investigated in patients with exacerbated asthma due to rhinovirus infection and it was found that it was able to reduce symptom burden, improved lung function and reduced the need for additional therapy; furthermore, it was able to stimulate the innate immunity this effect being proven with the increased serum levels or ISGs mRNA [22,23].

Another potential therapeutic indication for the inhaled recombinant IFN-β is represented by exacerbated COPD. This approach is supported to date by the experimental results coming from an in vitro study performed with monocyte-derived macrophages (blood), alveolar macrophages, and bronchial epithelial cells (endobronchial sampling) which were collected from healthy controls and COPD patients and exposed to influenza virus infection. Treatment of these cells with recombinant IFN-β prior to the experimental infection resulted in protective effect against viral intracellular infection which was concordant in both blood- and lung-derived cells and which has a post-effect of up to 72 h from interferon cessation [24].

4. Inhaled beta-interferons for SARS-COV2 infection

Inhaled IFN-β was more recently advocated as a potential anti-COVID-19 therapy based on its most potent antiviral properties among other type I IFNs and based on confirmation of the inhalation route as the most plausible for dosing in this setting in patients with milder forms of lung disease, whereas in patients with more severe multi-organ involvement intravenous or subcutaneous administration were recommended. In this latter category of patients, it is supposed that a more 'systemic' antiviral response is needed [25–27].

In vitro, in a study on the IFN-β dynamics during SARS-COV and SARS-COV2 infection, respectively, it was demonstrated that Vero and Calu 3 cells infected with SARS-COV2 and pretreated with IFN-β had a lower intracellular viral load compared to the same cell types incubated with SARS-COV [26]. Furthermore, the formulation of IFN-β-1a (SNG001) was also found to exert antiviral effects on SARS-COV2 variants (UK, South Africa), in vitro after infecting Vero E6 cells [28].

In vivo, in the animal model of SARS-COV2 infection, it was not the IFN-β but IFN-α A/D which was tested in a prophylaxis approach (intranasal administration prior to SARS-COV2 infection) and it was found that it had the potential to reduce viral replication and to accelerate viral shedding from the lungs [29].

The inhalation route of IFN-β is currently explored in clinical trials in SARS-CoV-2 infected patients [30]. The rationale for nebulized therapy is to achieve a robust local antiviral response by sufficiently high concentrations of interferon-β in the lungs while limiting systemic exposure to interferon-β. Targeting the surface epithelial cells of the lungs which represents the primary site of SARS-CoV-2 virus infection can induce the expression of interferon stimulated genes directly and indirectly involved in the antiviral response. Furthermore, in an in vitro model of SARS-COV2 infection using human bronchial cells, the addition of both INFI and INF III resulted in an upregulation of 'antiviral' genes and in an inhibition of viral replication and release. As viral release after multiplication occurs at the apical (intraluminal) site of bronchial cells, this further supports the administration at this level of INFs [8] The need to explore the efficacy and safety of the two recombinant IFN-β isoforms (IFN-β-1a and IFN-β-1b) via nebulization has become rather imperative due to COVID-19 pandemics and due to limited number of therapeutic options especially for severe forms of the disease.

There are two formulations of IFN-β namely 1a and 1b, the former being more advanced in its clinical development as a therapy for SARS-COV 2 infection.

4.1. IFN-β-1a

The novel recombinant IFN-beta-1a formulation developed for inhalation use (SNG001) by Synairgen PLC, was aimed for direct delivery to the lungs via nebulization. It is produced in mammalian cells and has a higher specific activity compared to interferon beta-1b [30]. This compound is already in use in patients with multiple sclerosis, demonstrating long-term safety and efficacy when administered systemically [31].

So far it was investigated in a phase 2 study, a randomized, double-blind, placebo-controlled pilot trial (SG016) in COVID-19 are already available [30]. Nebulized SNG001 (6MIU IFN-β) was given once daily for 14 days in patients with confirmed SARS-COV2 infection and admitted in the hospital for symptoms in addition to the usual care. A follow-up period of up to 28 days was also included in the study design. Endpoints of efficacy included likelihood (odds ratio) of improvement of the Ordinal Scale for Clinical Improvement (OSCI) WHO scale, time to recovery, time to discharge, time to severe disease or death, risk of severe disease or death. Intention to treat analysis included 98 patients (50 in the treatment (SNG001+ usual care), and 48 in the placebo (usual) care group). Mean age was 56.5 years in the treatment group and 57.8 in the placebo group, most of the patients in both groups were males and in terms of disease severity at baseline 56% respectively 75% of patients required supplemental oxygen at the time of hospital admission. Comorbid conditions such as hypertension, diabetes, or chronic lung disease were present in 27 patients in the treatment group and 26 patients in placebo group. Duration of symptoms at the time of hospital admission was 9.5 in treatment and 10 days in placebo group.

SNG001 significantly enhanced the likelihood of 'symptomatic' recovery to a score of 1 on the OSCI (the point where patients had 'no limitation of activities') without rebound (OR 2.32, $p = 0.033$) and the likelihood of 'general' recovery and reduced the risk of progression to severe disease or death (OR = 0.28, $p = 0.64$). However, there was no significant impact of the evaluated treatment on time to hospital discharge by day 28 or in the odds of intubation or the time to intubation or death [30,32]. Because the study was not adequately powered to analyze mortality outcomes, larger clinical trials are requested in this direction [30]. Over the 14-day treatment period, the SNG001 group had a greater improvement in breathlessness and the total Breathlessness, Cough, and Sputum Scale (BCSS) score. The same study also included a Home Cohort with patients having milder form of disease and who were given similar therapeutic regimens. Preliminary data indicate that maximum therapeutic benefit with IFN-β was obtained in patients with marked or severe breathlessness at the time of treatment initiation (were three-fold more likely to recover than those on placebo, a similar finding being observed in the pooled cohort data analysis of SG016 trial [33].

Safety analysis demonstrated that 54% of the hospital cohort patients in the treatment group respectively 60% of those in placebo group experienced treatment-emergent adverse events. The incidence of treatment-emergent adverse events was 28% in placebo and 15% in the treatment groups. The published data do not include a listing of these events based on the organ/tissue involved but are expected to be reported with the pooled-analysis.

Due to the exclusion of ventilated patients or patients in the intensive care unit (ICU), the SG016 study population was overall at less severe stage of COVID-19 compared to other trials and it would be interesting to have efficacy data from patients with more severe forms of disease [34].

4.2. IFN-β-1b

IFN-β-1b is also considered for further clinical development in SARS-COV2 infection.

IFN-β-1b has been shown to possess antiviral and immunomodulatory properties. Its biological properties are mediated by specific cellular receptors which induces the release of specific mediators, decreases affinity, stimulates the internalization, and degrades the interferon gamma receptor. Studies in healthy volunteers and rhesus monkeys did not reveal acute toxicity. Only few data are available for this compound as a monotherapy. In fact, case series of four critical patients with severe SARS-COV2 infection receiving another type of IFN-β, IFN-β-1b, and inhaled via cascade impactor to mimic the lung nebulization. Clinical improvements after 7–16 days of IFN dosing were reported along with the reduction in biomarkers of systemic inflammation [34].

IFN-β-1b was also evaluated in a combined regimen with other antivirals: inhaled IFN-β-1b at a dose of 8 MIU (0.25 mg), twice a day for 5 days through a vibrating mesh aerogen nebulizer, was assessed in combination with oral favipiravir

compared to hydroxychloroquine (400 mg twice per day on day 1, then 200 mg twice per day for 7 days) as a standard of care treatment group in adults hospitalized with moderate to severe COVID-19 pneumonia [35]. There were no differences in terms of clinical outcomes, inflammatory profile at hospital discharge at 14-days, overall length of hospital stay, overall 14-day mortality, transfers to the ICU or discharges but this might be due to the fact that the most appropriate dosing period for IFN-β-1b was actually missed in such patients [35].

5. Interferon-β in pediatric population with COVID-19

The recent emergence of the delta variant of SARS-COV2 was associated with an increasing incidence of COVID-19 in pediatric population. According to a recent review of the COVID-19 disease features in children, the most morbid forms were found in very young children (under 3 years of age) and in those with concomitant chronic diseases [36,37].

As far as the pediatric COVID-19 is concerned, inhaled INF-β might be a potential therapeutic approach reserved for those with severe forms of disease and bacterial superimposed infection. This is a hypothesis which however still needs to be confirmed as the pathogenic rationale is only available for interferon-alpha: in a study evaluating serum INF-α levels in children referred to the emergency room due to febrile viral or bacterial infections, these were overall demonstrated, the latter category of infections being associated with the most decreased values [38]. On the other hand, INF-β is currently used systemically in children with relapsing multiple sclerosis, and therefore inhalation route of this medication is worth being explored in severe pediatric SARS-COV2 infection [39].

6. Conclusions

The existing data despite coming from limited samples of patients with SARS-COV2 infection point out toward IFNs-β as potentially efficacious inhaled therapies in this disease. Most of the clinical and experimental data are available for IFN-β-1b formulation and indicate good premises for efficacy and suitability for increasing the antiviral defense during infection and disease. However further clinical data are needed in patient with severe forms of disease and for a better understanding of the safety profile.

7. Expert opinion

INFs-β might represent a promising therapy for COVID-19 disease. It is able to interfere with disease progression and consequently to speed up the recovery. It is also hoped that it can reduce the risk of development of pulmonary sequelae in patients with extensive pulmonary disease but this can only be documented with a long-term follow up of the cohorts already studied or under study in clinical trials.

Another issue which needs to be clarified is relate to the characterization of the appropriate formulation for particular circumstances of use or for better chemical properties. For example, IFN-β-1b would be more appropriate for domiciliary use? for once daily dosing? Is more stable? which would be the most appropriate excipients in the inhalation solution ? What about 1a type?

Treatment period is another aspect which needs further studies and related to this is which is the period in the disease course when such therapy would have the maximal efficacy: is it better to identify a risk profile in patients with milder/asymptomatic disease and to give IFN-β at the time of diagnosis? Would it on the contrary be more appropriate to preserve this therapy to more critical patients with high systemic inflammation load? If latter would be an interesting approach which would be the biomarkers to be used to monitor the anti-inflammatory efficacy for example? [32].

Combined regimens with other antiviral drugs or with drugs able to enhance the IFN activities represents another path yet to be explored in more depth. Existing clinical data demonstrate the synergic effects of adding antivirals such as favipiravir to IFN-β, whereas other studies are focusing on compounds such as for example azithromycin which is able to enhance endogenous IFN signaling pathways and thus to contribute to an extra effect to the exogenous counterpart [13,40].

Furthermore, the results of the ongoing SG018 Phase III trial, together with the other ongoing studies on nebulized IFN, will hopefully provide the missing pieces of this therapeutic puzzle.

Declaration of Interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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