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Inhaled Interferon for Asthma Treatment (NR): A narrative review

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Abstract

Although various therapeutic strategies, such as inhalant beta-2 agonists, corticosteroids, anti-leukotrienes, and even novel inclusion of active biological agents in the management of asthma have been established, as asthma is a global issue and chronic in nature, the search for potential new tools to the arsenal continues to this day. Remarkable progress has recently been achieved in identifying the pathophysiology and potential value of interferons (IFNs) in managing allergic asthma. This narrative review attempts to precisely demonstrate the possible use of inhalant IFNs in differing asthmatic conditions by simplifying and concluding studies published between 1995 and 2021. Review findings indicate that IFN lambda and gamma could be utilized as primary tools in asthma management, while IFN beta can be used as an adjuvant therapy for viral-induced severe asthmatic exacerbations.

Keywords: Inhaled interferons; Asthma management; Asthma exacerbation; Interferon gamma; Interferon beta; Interferon lambda

1. Introduction

Asthma is a highly prevalent, chronic respiratory disease that impacts millions of people worldwide and causes thousands of deaths every year [1]. Irrespective of disease severity or management, asthmatic patients could experience acute exacerbation attacks, often triggered by respiratory infections [1]. For decades, physicians relied on bronchodilators to treat asthmatic symptoms [2]. Although steroids were also well known to control airway hyperreactivity, their side effects caused them initially to be used only in the most severe cases [2]. Thereafter, the availability of effective aerosol steroid preparations addressed the chronic unchecked inflammation that leads to airway remodeling [2]. However, in some patients, asthma may be resistant to corticosteroids and there is a need for alternative therapies [2] to be used as primary tools.

Over the last few decades, there has been advancement in the idea of employing interferons (IFNs) as therapeutic agents to treat a variety of asthmatic conditions. The interferon family represents a group of cytokines that play a central role in protecting against and exacerbating various infections and pathologies, including asthma [1]. Type I and III IFNs in particular play an indispensable role in the host immune system to fight off pathogens, which seems to be altered in both pediatric and adult asthmatics [1]. Evidences suggest reduced innate activity of antiviral IFN-β in severe asthmatics [3, 4]. There are documented cases of acute asthmatic exacerbations induced by viral respiratory infections such as rhinovirus or RSV by the mechanism of decreased innate interferon [3, 4, 5]. Moreover, a similar reduction in innate IFN activity due to viral infections has also been shown in pregnant patients [6]. Evidence also suggests that even early developmental constraints of innate type I or III IFNs lead to severe respiratory tract infections and subsequent

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development of asthma during infancy [7]. Both steroid-naïve and steroid-treated groups of asthmatic children, as opposed to healthy control subjects, show significantly lower serum levels of IFN-γ [8].

Therefore, by reviewing various experimental and clinical studies using the journal search engines ClinicalTrails.gov, Embase, PubMed, Google Scholar, ScienceDirect, and Cochrane, this article summarizes a broad application of inhaled interferon therapy in Asthma. This will shed light on the novel opportunities for using inhaled IFNs as one of the primary treatment options in the management of asthmatic patients.

2. Background

Allergic asthma, a chronic disease of the airways, has been documented at an increasing rate worldwide [9]. The pathophysiology is characterized by chronic airway hyperresponsiveness (AHR) and inflammation due to exposure of the airways to several harmless allergens including proteins from house dust mites, molds, tree and grass pollens, and animals with the increased production of serum IgE, and Th2 cytokines involving multiple cells such as dendritic cells (DCs), eosinophils, mast cells, and T lymphocytes [9].

Interferon (IFN) proteins are a family of cytokines secreted by host cells in response to pathogens and function to activate proper cell defense mechanisms by surrounding uninfected cells [10]. According to their respective receptors, IFNs are classified into three types (Type I, Type II, and Type III) [10].

Type I IFNs, the largest IFN family in humans, bind to IFN-α/β (IFNAR1, IFNAR2) cell receptors acting as messengers to neighboring uninfected cells of invading pathogens [10]. It has been postulated that the main function of this IFN is to inhibit viral protein synthesis by affecting eukaryotic translation initiation factor 2a (eIF-2a) [10].

Type II IFNs are produced by activated T cells and natural killer (NK) cells, and bind to the IFN-γ receptor complex (IFNGR1, IFNGR2) resulting in increased inflammation via inflammatory cells recruitment [10].

Type III IFNs which include IFN-λ1, IFN-λ2, IFN-λ3, and IFN-λ4 bind to the receptors IFRL1 and IL-10R2 [10]. They are associated with the JAK-STAT pathway and are produced when the host detects pathogen-associated molecular patterns (PAMPs), similar to Type I IFNs [10].

IFNs have been shown to down-regulate inflammatory responses through various pathways that can help in controlling airway inflammation and reduce the recruitment of pro-inflammatory cells. In a 2015 Journal of Innate Immunity, the IFN-λ synthesized by epithelial cells, macrophages, and dendritic cells result in the production of anti-inflammatory cytokines IL-10 and TGF-β by T regulatory cells [9]. Additionally, an inverse link between IFN-λ and the severity of allergic asthma and asthma exacerbation was observed in humans by the regulations of Th17 and Th2 responses [9]. IFN-λs also can influence dendritic cells (DCs) and their product, IFN-λs-DCs, can directly affect T cells through inhibition of the T helper 2 cell (Th2) responses [11].

A paper written by Nakagome in 2009 showed IFN-γ acts as an immune-modulating cytokine and attenuates Ag-induced immune responses in the lung by suppressing the functions of CD11c+ APCs and CD4+ T cells [12]. IFN-γ attenuated the indicators of a Th2-type response such as eosinophilic inflammation, IL-5 & IL-13 production in the lung, IgE production, IL-17, and IFN-γ itself [12]. IFN-γ suppressed allergic airway inflammation not only when administered before systemic sensitization but also when delivered during the effector phase of an allergic immune response [12].

Djukanovic and colleagues discovered in 2014 that individuals with severe asthma have lower endogenous IFN production, therefore adding exogenous IFN increased innate immunity and improved viral clearance via modifying the type 2 inflammatory response to viral infection [13].

2.1. Impaired antiviral response of interferon in severe therapy-resistant asthma (STRA)

A 2012 study on STRA in children showed a reduction in innate IFN responses to RVs infection [5]. This ex-vivo study involved the use of bronchial epithelial cell (BEC) cultures. These cultures were established using cells collected from bronchial brushings of children diagnosed with severe therapy-resistant asthma (STRA). These cells demonstrated a diminished production of IFN-β, IFN-λ1, and IFN-λ2/3 mRNA when infected with rhinoviruses (RVs), in contrast to control cells derived from non-atopic non-asthmatic (NANA) individuals [14].

Following infection, a significant decrease in the production of all IFN mRNA subtypes was observed in STRA cells compared to NANA cells at the 24-hour mark. The median fold differences for IFN-β were 282 with RV16 ($P<0.01$), and

23 for RV1B (P<0.01) [14]. Beyond the 24-hour point, a declining trend was noted in RV1B induced IFN-β, IFN-λ1, mRNA levels, and IFN-λ2/3 mRNA levels at 24 hours with RV1B loads at 48 hours [14].

The study points out the association of impaired IFN production in STRA BECs with increased RV viral replication [14]. Thus, this study lends support to the hypothesis that exogenous IFNs β (beta) & λ (lambda) may assist in lowering airway inflammation driven by viral infection in asthmatic patients, thereby lowering the likelihood of an asthma exacerbation.

2.2. Animal study shows improved asthma control with inhaled recombinant IFN-λ

A study published by Jina Won and colleagues showed a recombinant IFN- lambda (rIFN-λ) induced reduction of Th2-mediated inflammation in the respiratory tract of 20 asthmatic mice [15]. The respiratory tract cells were made to undergo the OVA challenge, resulting in higher total lung resistance and increased Th2 cytokine secretion (TSLP, IL-33) in Bronchoalveolar lavage fluid [15].

Asthmatic mice were then administered recombinant IFN-λ2/3 via nebulization and alterations in methacholine (mch) induced airway resistance and histopathology findings were observed [15]. Interestingly, methacholine-induced increases in total lung resistance were not observed in IFN-λ-delivered asthmatic mice and there was significant suppression of innate lymphoid cell (ILC), ILC2, and ILC3 population in the lungs of asthmatic mice [15].

Furthermore, IFN-λ2/3-treated asthmatic mice showed a significant reduction in cytokines generated by Th2 (IL-4, IL-5, IL-13) and Th17 (IL-17A, IL-17E) [15]. An increase in IFN-λ-induced anti-inflammatory response was noted in the lungs of in vivo allergic asthmatic mice through the activation of IL-10 release and the subsequent secretion of CD4 + T cells [15].

This study suggests that inhaled exogenous IFN-λ levels in the respiratory tract can help asthmatics regulate allergic inflammation in the lungs [15]. Hence it provides new opportunities for more effective control of the pathogenesis of allergic inflammation in the lung.

2.3. IFN-β (SNG001) nebulization treatment to lessen asthma flare-ups triggered by viral infection

In this Phase-2 study from 2014, which was randomized, double-blind, parallel, and placebo-controlled, IFN-β (SNG001) was tested on participants (n = 147, aged 18-65 years). These participants, who were on inhaled corticosteroids for their asthma and had a history of virus-related exacerbations, were evenly distributed after they exhibited symptoms of an upper respiratory tract infection within 24 hours [13].

After receiving either a placebo or inhaled IFN-β at a single dose of 6 mIU per day for 14 days, patients were reviewed for daily upper and lower respiratory symptoms using asthma control questionnaire score (ACQ- 6), peak expiratory flow (PEF) measurement and the BTS score (British Thoracic Society Steps 2–5) [13]. The main goal of the study was to monitor the average shift in the ACQ-6 score from the starting point to Day 8 in the population subjected to the modified intention-to-treat (mITT) approach [13].

Regrettably, in the population subjected to the modified intention-to-treat approach, the IFN-β treatment didn't have a significant impact on the primary endpoint, even though it did improve the recovery of morning peak expiratory flow (average difference between groups, 19.47 L/min; 95% confidence interval [CI], 1.62–37.31; P = 0.033) [13]. However, in the more challenging-to-treat asthmatic groups (BTS Step 4-5) (n = 27 IFN-β; n = 31 placebo), there was a significant increase in the ACQ-6 score in the placebo group compared to the IFN-β group (P = 0.004) [13].

Additionally, the evaluation of biomarkers in blood and sputum indicated alterations that aligned with increased antiviral activity and related reduction of pro-inflammatory reactions in patients undergoing IFN-β treatment [13].

Even though this study didn't achieve its main goal, it implies that inhaled IFN-β could be a potential therapy for the worsening of asthma triggered by viruses in individuals with asthma who are hard to treat. Therefore, additional research is required in cases of more severe asthma (BTS Step 4-5) [13]. Though some encouraging findings are presented in the study, larger, more thorough investigations would be necessary to confirm the clinical use of inhaled IFN-β in the treatment of virally-induced asthma symptoms [13].

2.4. Trial of On-demand Inhaled IFN-β1a (AZD9412) in Severe Asthmatics

AstraZeneca conducted another study from the period of 2015 - 2019, which was a Phase 2 Randomized double-blind, placebo-controlled, multicenter trial of On-demand inhaled interferon beta **IFN-β1a (AZD9412**) in preventing severe asthmatic exacerbation induced by viral infection [16].

Patients with severe asthma (GINA 4-5; n = 121) who were experiencing symptoms of an upper respiratory tract infection were randomized to undergo a 14-day treatment of either a daily nebulized dose of AZD9412 or a placebo [16]. The primary outcome of the study was to evaluate if on-demand inhaled IFN-β1a (AZD9412) was effective in preventing severe asthma exacerbations after a symptomatic upper respiratory tract infection (URTI) during the initial 14 days of treatment [16].

However, the study was ended earlier than planned due to a surprisingly low rate of exacerbation, as per a pre-scheduled interim analysis [16]. Numerically, AZD9412 did not reduce severe exacerbation rates [16]. The study was not statistically significant as well - **p value 0.64 with (2-sided) 95% 0.43 to 3.85** [16]**.** Additionally, AZD9412 did not result in a reduction of the ACQ-6 asthma symptom scores or the usage of reliever medications [16].

Conversely, an analysis of the area under the curve (AUC) using the ANCOVA method for changes from the baseline during Days 1-7 indicated that AZD9412 enhanced lung function (specifically, morning peak expiratory flow; mPEF) by 19.7 L/min (p-value - 0.010; (2-sided) 95% CI [4.66 to 34.05]) [16]. According to an exploratory post hoc analysis, AZD9412 significantly improved mPEF in patients who had high blood eosinophil counts (>0.3 × 109 /L) at screening and a low relative change in serum interleukin-18 at the pretreatment baseline [16].

To summarize, the use of AZD9412 on an as-needed basis didn't significantly cut down the frequency of exacerbations, but it did help mitigate the decline in mPEF caused by upper respiratory tract infections [16]. The study also suggests that patients with severe asthma who have high blood eosinophils or low serum interleukin-18 response may be suitable subgroups for further evaluation of inhaled IFN-β1a (AZD9412) efficacy [16]

2.5. Nebulized interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection

Although this study is not based on asthmatic patients, it supports the theory that asthma exacerbations due to viral infection can be treated with inhaled interferon beta-1a (SNG001) [8]. The study was conducted as a randomized, double-blind, placebo-controlled, phase 2 pilot during the period 2020 to 2021 [17].

Eligible patients were randomly assigned (1:1) to receive inhaled nebulized IFN-β1a (SNG001) or placebo [17]. The primary aim of the trial was to record the recovery of study subjects throughout a 14-day treatment period with a WHO Ordinal Scale for Clinical Improvement (OSCI) score of 1 (no limitation of activities), compared to placebo controls [17].

After treatment, the results demonstrated a significant likelihood of progress on the OSCI scale. The improvement was more than double in the SNG001 group compared to the placebo group on either day 15 or 16 (odds ratio [OR] 2·32 [95% CI 1·07–5·04]; p=0·033), and it was more than triple on day 28 (3·15 [1·39–7·14]; p=0·006) [17].

During the 14-day treatment duration, the likelihood of recovery was more than double for patients in the SNG001 group compared to those in the placebo group (21 [44%] out of 48 with SNG001 versus 11 [22%] out of 49 with placebo; hazard ratio [HR] 2•19 [95% CI 1•03-4•69]; p=0•043) [17].

Secondary results encompassed the alteration in the Breathlessness, Cough and Sputum Scale (BCSS) score, along with the safety and acceptability of the drug under investigation [17]. Patients receiving SNG001 showed a more substantial enhancement in the secondary outcome analysis of the overall BCSS score compared to those on placebo throughout the 14-day treatment span (the difference between SNG001 and placebo was -0•8 [95% CI -1•5 to -0•1]; p=0•026) [17].

Patients hospitalized due to COVID-19 infection seemed to accept SNG001 well, a medication that has been previously studied and found to be well received in patients with asthma. A range of clinical results indicate a favorable trend in response to the treatment with SNG001 [17].

Consequently, two research studies on interferon beta-1a (SNG001) have demonstrated the advantages of employing inhaled recombinant IFN beta in managing severe asthmatic flare-ups triggered by viruses [13, 17].

2.6. Effects of nebulized recombinant interferon-gamma (rIFN-γ) in asthmatic airways

In this 1995 study, five nonsmoking adults with mild atopic asthma were compared pre and post-nebulization with rIFN-γ to study its effects on asthmatic airways [18]. Nebulized recombinant IFN-y was administered in an open-label trial with increasing doses on specific days [18].

Subjects underwent baseline spirometry and methacholine challenge, followed by fiberoptic bronchoscopy with Broncho alveolar lavage (BAL) [18]. All baseline measurements were repeated after the last dose of rIFN-y using spirometry and peak expiratory flow rates [18].

Data obtained at baseline and after rIFN-γ treatment were compared using Student's t-test for paired values [18]. The study had sufficient power to detect significant differences in FEV1, percent predicted FEV1, and BAL fluid white blood cells [18].

Results showed no significant differences from baseline in clinical symptom scores, FEV1, and morning peak expiratory flow rates [18]. All patients tolerated the nebulized rIFN-y well, with only a transient mild cough noted during treatment in three patients [18].

The effectiveness of the delivery system was demonstrated by the recovery of IFN-γ after, but not before, treatment in BAL fluid ($p < 0.001$) [18]. More importantly, nebulized rIFN-γ was effectively delivered to the respiratory epithelium and exerted a biological effect as measured by upregulation of mRNA for IP-10, an IFN-γ–specific protein induced in activated alveolar macrophages [18].

Treatment with rIFN-γ did not result in any significant increase in airway inflammation [18]. Interestingly, four of the five patients had a decrease in the percentage of BAL eosinophils [18]. The study provides valuable insights into the effects of nebulized rIFN-γ in asthmatic airways. However, it has several limitations, including a small sample size, lack of a control group, and an open-label design [18].

2.7. Prevention of antigen-induced eosinophil recruitment by Aerosolized rIFN- γ in asthmatic guinea pig trachea

In a different 1997 study published in China, following its asthmatic sensitization with Rhizopus Nigricans and divided into six groups, 30 guinea pigs received separately aerosolized rIFN-γ at concentrations of 5×10^{4}, 20×10^{4}, and 40×10^{4} as well as normal saline and beclomethasone dipropionate (BDP) in their tracheas **[**19**]**.

The results showed a decrease in airway resistance ($p < 0.01$) and a reduction in the rates of positive provocation in the groups treated with 40×10^{4} rIFN-γ and BDP, compared to the group treated with normal saline ($p < 0.05$) [19]. The administration of BDP and aerosolized rIFN-γ (40×10^{4}) also lessened the infiltration of eosinophils in the trachea induced by fungus, but did not affect the infiltration of other cells [19]. In the bronchoalveolar lavage fluid (BALF), both the count of Eos and the levels of eosinophil cationic protein (ECP) were found to be lower in the rIFN-γ group than in the other groups [19].

The research inferred that the inhalation of rIFN-gamma (40×10^{4}) could potentially diminish airway inflammation and intervene in asthma episodes by preventing the infiltration of Eos and ECP in the airways [19]. Unfortunately, because the complete study was published in Chinese, comprehensive evidence and statistics were not readily available.

Additional studies involving phase 1 trials with larger samples to assess the safety and efficacy of inhalant IFN-γ needed to be conducted to confirm its use as a primary tool.

3. Discussion

The examination of various studies has assisted in pinpointing potential uses of inhaled interferons for specific types of asthma. Primarily, there's evidence suggesting a decrease in the production of innate interferon during severe asthma triggered by viruses, especially concerning the interferon subtypes IFNβ and IFNλ [14]. Consequently, we explored studies involving exogenous inhalant interferons in asthma-related contexts. IFNλ, a newly discovered subtype, demonstrated reduced TH-2-mediated inflammation through exogenous nebulization in an in vivo animal study [15]. However, further ex vivo studies in human cells and phase 1 human trials are necessary to confirm and analyze the efficacy and safety of inhaled IFNλ as a potential primary tool in asthmatic therapy.

Secondly, unlike IFNλ, IFNβ did not directly reduce asthmatic airway inflammation. However, phase 2 trials with IFNβ1a (SNG001) showed efficacy in shortening the duration and intensity of viral-induced severe asthmatic exacerbations in adults [13, 17]. Additionally, the trial involving inhalant IFNβ1a (AZD9412), although terminated due to a low exacerbation rate, demonstrated greater improvement in morning peak expiratory flow (mPEF) in patients with high blood eosinophil counts and low serum interleukin-18 levels compared to pretreatment baseline [16]. Therefore, inhalant IFNβ may serve as an adjuvant therapy specifically for acute viral-induced severe asthma (e.g., BTS score 4-5) [13]. To validate its efficacy and safety, phase 3 trials for SNG001 and repeat phase 2 trials for AZD9412, particularly in patients with high blood eosinophils or poor serum interleukin-18 response, should be conducted [16].

Lastly, studies involving inhaled interferon-gamma (rIFNγ) demonstrated reduced airway inflammation and prevention of asthmatic attacks by inhibiting localized eosinophils and ECP infiltration [19]. Inhaled rIFNγ also exhibited an acceptable safety profile in adult asthmatic patients [18]. Thus, inhalant IFNγ appears to be a viable primary strategy for managing asthma. Additionally, assessing the cost-effectiveness of incorporating inhaled interferons into asthma treatment strategies is essential.

Abbreviations

IFNs – Interferons
rIFN – recombinant Interferon
IFNβ – Interferon beta
IFNγ – Interferon gamma
IFNλ – Interfeon lambda
TGFβ – Tumor Growth Factor beta
RSV - Respiratory syncytial virus
RV – Rhinovirus
URTI – Upper Respiratory Tract Infection
AHR - Airway Hyperresponsiveness
APCs- Antigen Presenting Cells
PAMPs - Pathogen-Associated Molecular Patterns
STRA - Severe Therapy Resistant Asthma
NANA - Non-Atopic Non-Asthmatics
BDP - Beclomethasone Dipropionate
BECs – Bronchio-Epithelial Cells
BAL – Bronchoalveolar lavage
TSLP – Thymic stromal lymphopoietin
ILC- Innate Lymphoid Cell
IL – Interleukin
ACQ score – Asthma Control Questionnaire score
BTS steps – British Thoracic Society Steps
BCSS - Breathlessness, Cough and Sputum Scale
OSCI score - Ordinal Scale for Clinical Improvement score
AUC – Area Under Curve
PEF – Peak Expiratory Flow meter
FEV1 – Forced Expiratory Volume in 1 second
ECP - Eosinophil cationic protein

4. Conclusion

Inhaled interferons offer a promising approach for asthma treatment. Reviews of existing studies highlight the potential of inhaled IFNλ as a primary medication for asthma and viral-induced exacerbations. Additionally, inhaled IFNγ may serve as a major tool for managing eosinophil-mediated hyper-responsive airway inflammation. However, further human clinical trials are needed to assess drug (IFNλ and IFNγ) efficacy and safety. On the other hand, inhaled IFNβ (SNG001, AZD9412) could be used as an adjuvant therapy for severe asthmatic exacerbation caused by viruses. Large-scale Phase 2 and 3 clinical trials are necessary to support its use. Considering asthma's chronic nature, the long-term safety and cost-effectiveness of inhaled interferons should be evaluated as well.

Compliance with ethical standards

Disclosure of conflict of interest

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